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TITLE: High Resolution Diffusion Tensor Imaging of Cortical-Subcortical White Matter Tracts in TBI

PRINCIPAL INVESTIGATOR: Deborah M. Little, Ph.D.

CONTRACTING ORGANIZATION: University of Illinois, Chicago
Chicago, IL 60612

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Deborah M. Little PhD

Email: little@uic.edu

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809 S Marshfield Rm 606
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14. ABSTRACT
The most significant finding to date is the identification of three potential biomarkers of closed head injury. Although 20 additional subjects are required to complete data collection, our preliminary analyses have shown that thalamic projection fibers in a subgroup of 12 controls and 24 patients with TBI are sensitive to injury and correlate with cognitive function (see Little et al Neurology, 2010). The second year has focused on developing and validating methods to characterize integrity of cerebellar and brain stem fibers. An additional publication has come out of the neuropsychological data and is included. Four additional manuscripts are presently being prepared for submission (expected by 12-2010). Also, the work has been highlighted in 10 invited talks, including a joint DoD, NIH, and VA sponsored conference on mild TBI as part of ATACC. We are well head of schedule and are excited at the significant contributions being made as a result of this award.

15. SUBJECT TERMS
Traumatic brain injury, diffusion tensor imaging, executive function

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Table of Contents

Introduction

The ***overall objective*** of the proposed research is to validate high resolution diffusion tensor imaging (DTI) as a diagnostic tool that would allow better characterization of patients who have sustained a mild to moderate closed head type TBI. The ***general hypothesis*** guiding this work is that TBI results in sustained changes in the white matter microstructure that can be assessed using DTI and that it is this change in white matter that results in chronic deficits in cognition. Our specific aims are to characterize: (i) and quantify neuropathology in frontal, temporal, and basal ganglia regions in chronic TBI using both diffusion tensor imaging and structural magnetic resonance imaging; (ii) white matter integrity of the cortical-subcortical fibers connecting basal ganglia and frontal regions using fiber tractography; (iii) the role of short-range (cortical u-fibers), as compared to long-range WM fiber tract integrity in TBI; (iv) cognitive function in chronic TBI using a neuropsychological test battery focused on executive function and attention. In order to accomplish the proposed aims, we will recruit 25 healthy controls and 50 TBI patients with closed head injuries ranging from mild to moderate in injury severity who are a minimum of 6 months post injury. In addition to MRI and DTI imaging these patients will also undergo neuropsychological testing with a focus on executive function and attention tasks.

Body

In the funded grant, we proposed to accomplish a number of concrete tasks by the completion of Year 2. These include (1) Completing all required administrative approvals and university approvals for the initiation of new research and continuing review at the completion of Year 2, (2) obtaining continuing approval of human subjects approvals through the Army, (3) collect 25 participants of data in Year 2 to add on to the 25 collected in Year 1, (4) continue validation and quality assurance of the imaging protocols, (5) continue analysis on participants and development of new methods on the first 50 subjects collected. All of these items have been completed. We have included the original statement of work below as well as the current and specific status of each.

Work to be Accomplished with Outcomes Identified at Each Stage

Please note that the original scope of work focused on specific tasks and not research accomplishments. As such, per the annual report guidelines and review requests in this revised annual report we have included the detailed scope of work but then have included a specific discussion and review of how the work conducted to date addresses the specific aims of the research. We hope this adequately addresses any remaining concerns.

SOW Year 1

- Complete all required administrative approvals and university approvals for the initiation of new research
- Status: Completed
- Obtain human subjects approval through the DOD
- Status: Completed
- Begin subject recruitment (this will continue through year 3) including talks by the PIs to local brain injury groups, patient advocacy groups and other physicians
- Status: Completed
- Hire a RA (at UIC this process takes between 2 and 3 months)
- Status: Completed. Michelle Siroko was hired as the project coordinator on this grant and continues in this capacity.
-
- Finalize the imaging protocol and complete quality assurance testing prior to the first subject

- Status: Completed
- Recruit and test 25 subjects. The testing will involve: characterization of TBI variables, characterization of postconcussive symptoms, a full neurobehavioral interview which will also assess any other mood or behavioral problems, neuropsychological testing and scoring of neuropsychological tests, MRI imaging including GRE, FLAIR, T2FSE, and DTI.
- Status: Completed
- Begin work on analysis protocols using these first 25 subjects as models. This will include a review of the literature to assess any new work that might highlight additional anatomical targets which have come to light since the grant application
- Status: Completed. Please see below for additional details.
- Carry out quality assurance testing on all image data that is acquired
- Status: Completed. Please see below for additional details.

SOW Year 2-Year 3

- Complete and obtain all continuing approvals for human subjects research
- Status: Completed. Please see below for additional details.
- Continue recruitment
- Status: Ongoing. Recruitment will continue until data from the last participant has been completed. The goal for each grant year was to collect 25 subjects. At the time of the annual report a total of 51 subjects had been recruited and had completed the experimental protocol. As such, this task is completed for Year 2 and ongoing for Year 3.
- Collect 25 subjects on the experimental protocol
- Status: Ongoing. Data collection will continue until data from the last participant has been completed. The goal for each grant year was to collect 25 subjects. At the time of the annual report a total of 51 subjects had completed the experimental protocol. As such, this task is completed for Year 2 and ongoing for Year 3. Please see below for additional details on subject recruitment and data collection.

SOW At the end of Year 2: Submit data from the first 50 subjects to Society for Neuroscience and Human Brain Mapping. Submit manuscripts on the sensitivity and specific of DTI for the assessment of neuropathology and cognition in TBI.
Status: Completed. Two abstracts were presented at the SFN. Additional details on manuscripts, analyses, and conclusions can be found in detail below.

SOW Detail: Human Subjects Assurances

All university approvals were obtained in the first quarter of the grant. Initial human subjects approvals were obtained on 06-16-08. The annual continuing review, which included no protocol deviations or adverse events, was approved via convened review on 06-23-09. Continuing approval through the Army was granted on 08-06-09 (A-15142). Since that time three amendments to the research have been approved through UIC and the annual continuing review was conducted on 6-21-2010. All continuing IRB approvals have been submitted and granted at both the level of the University and Army.

SOW Detail: Human Subject Recruitment and Screening

We have now screened over 200 subjects and have finished data collection on 51. Analysis of all proposed measures has been completed in 48 of 51 subjects. This includes an analysis of thalamic projection fibers, analysis of brain stem fibers, analysis of cerebellar fibers, and analysis of basal ganglia. We have sufficient power on these methods to begin manuscript preparation and plan to submit within the next month. These are detailed in Figure 1.

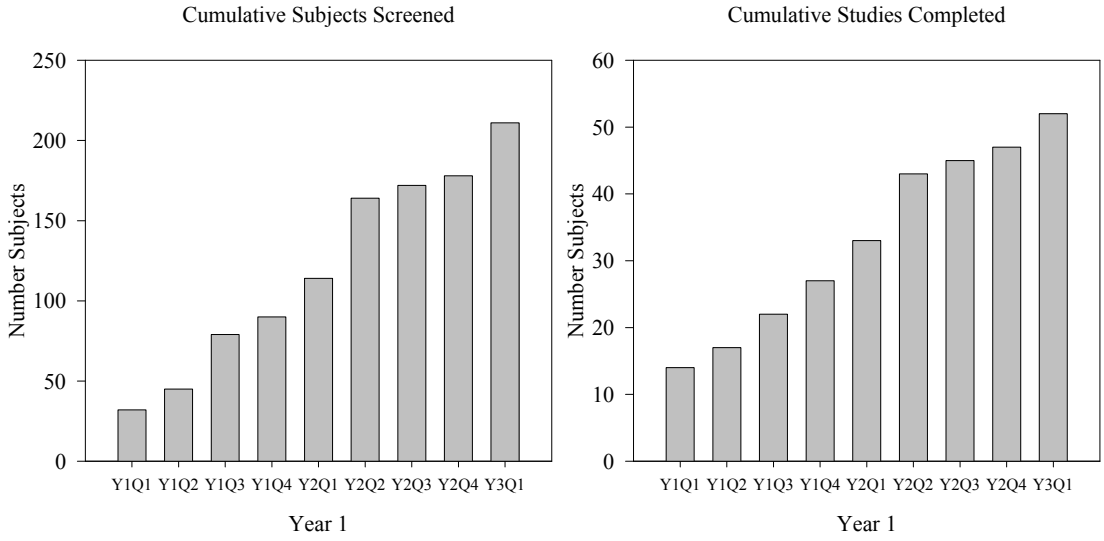

Figure 1. Numbers of subjects recruited and screened (left) and total number of subjects who have completed the experimental protocol (right) by grant quarter.

SOW Detail: Quality Assurance Data

Given the central role of high resolution imaging on the success of this grant, monthly quality assurance protocols are carried out on a phantom data set using the same pulse sequences as for the human data. The imaging parameters for this quality assurance protocol are: TR/TE=5000/64ms, b=0,1000 s/mm^2, diffusion directions=27, FOV=20x20cm^2, matrix=256x256, slice thickness/gap=3/0mm, slices=7, NEX=8, and acceleration factor=2.

As was reported for the last annual review, our quality assurance protocol proved valuable three times in the first year when changes in signal intensity and nyquist ghost were identified leading to service calls. The historical data are presented in Figure 2. As can be seen we have collected data as proposed one time per month. In months where problems were noted a second or third QA protocol was run to ensure the scanner had indeed been fixed. As can be seen the overall mean signal and ghost are quite stable with these exceptions noted. As such, there are no concerns with the data.

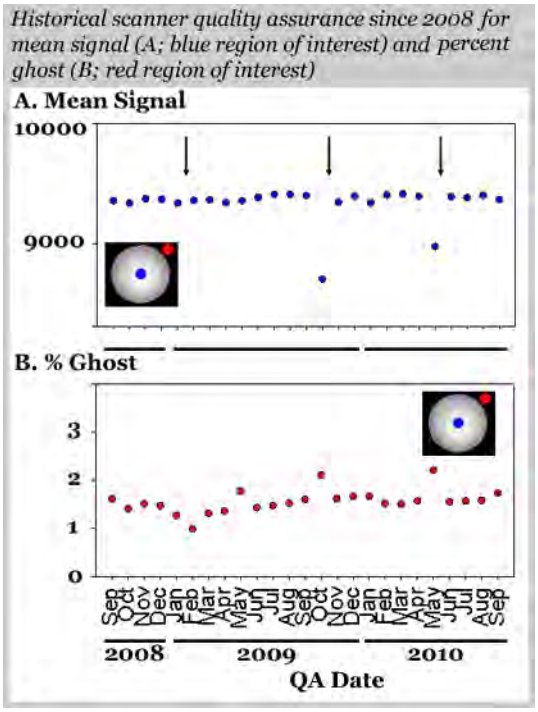

Figure 2. Quality assurance data on the scanner and coil including mean signal and percent nyquist ghost.

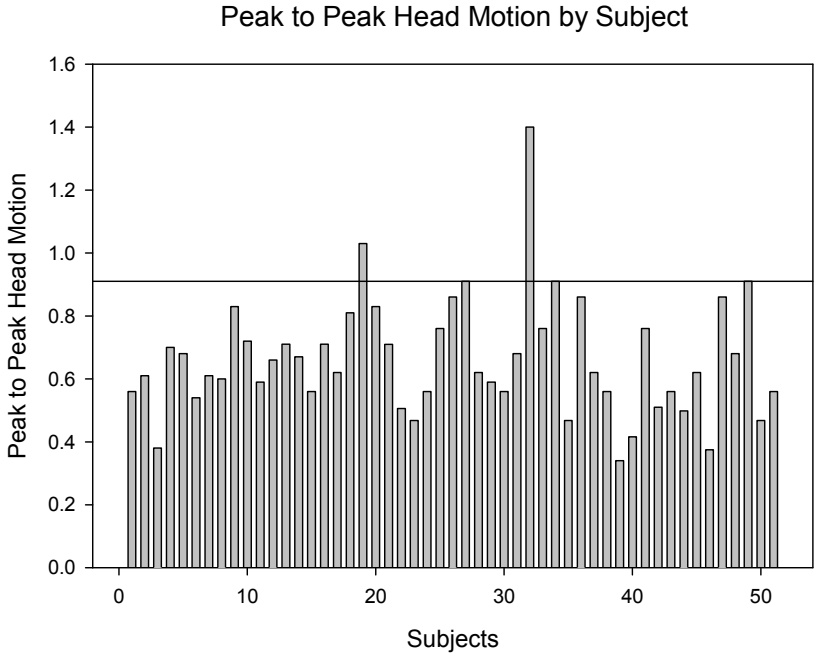

Figure 3. Head motion for each subject tested thus far.

Data from human subjects is assessed for each dataset. For human subjects noise and signal cannot be assessed in the same manner as our quality assurance data. As such, we use two indices. The first is peak to peak head motion as increased head motion will make the data unusable. Our threshold is 1 voxel of motion for a dataset to be included. In this study, the maximum motion allowable is 0.91 mm of in-plane movement. We present this information in the Figure below as peak to peak head motion for each subject. As can be seen, Subject 19 exceeds this threshold. Subject 27 would be considered borderline for inclusion and Subject 33 clearly will be excluded from group analyses in terms of the DTI data. These subjects can however be used for the volumetric analysis.

SOW Detail: Summary of findings to date and their relationship with proposed aims.

In order to address progress not only on the tasks required to test the hypothesis but also on the status of data analysis and how published and in progress works address the Aims of the grant we first review the proposed Aims of the grant. These were:

(i) to characterize and quantify neuropathology in frontal, temporal, and basal ganglia regions in chronic TBI using both diffusion tensor imaging and structural magnetic resonance imaging;
(ii) to characterize white matter integrity of the cortical-subcortical fibers connecting basal ganglia and frontal regions using fiber tractography;
(iii) to characterize the role of short-range (cortical u-fibers), as compared to long-range WM fiber tract integrity in TBI;
(iv) to characterize cognitive function in chronic TBI using a neuropsychological test battery focused on executive function and attention**.**

Each project summary detailed below directly addresses at least one if not more than one aim. These are identified following the summary of each grant and <u>underlined.</u>

Experimental Data Analysis Conducted to Date – Published Manuscripts

Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, Pliskin N, Gorelick PB. Thalamic integrity underlies executive dysfunction: Evidence from Traumatic Brain Injury. *Neurology* 2010; 74: 558-564 (PMID: 20089945). *(please see Appendix A)*

Summary:
High-resolution diffusion tensor magnetic resonance imaging described in detail in this grant application with a focus on subcortical fiber projections from the thalamus was conducted on 24 patients with a history of single, closed-head traumatic brain injury (12 each of mild TBI and moderate to severe TBI) and 12 age- and education- matched controls. Detailed neuropsychological testing with an emphasis on executive function was also conducted. Fractional anisotropy was extracted from 12 regions of interest in cortical and corpus callosum structures and 7 subcortical regions of interest (anterior, ventral anterior, ventral lateral, dorsomedial, ventral posterior lateral, ventral posterior medial and pulvinar thalamic nuclei).

Relative to controls, patients with a history of brain injury showed reductions in fractional anisotropy in both the anterior and posterior corona radiata, forceps major, the body of the corpus callosum and fibers identified from seed voxels in the anterior and ventral anterior thalamic nuclei. Fractional anisotropy from cortico-cortico and corpus callosum regions of interest did not account for significant variance in neuropsychological function. However, fractional anisotropy from the thalamic seed voxels did account for variance in executive function, attention, and memory. *Specific methodological details and findings are present in the appendix.*

Please note that this published manuscript in part addresses Aims 1 and 2.

Geary EK, Kraus MF, Pliskin NH, Little DM. Impairments in verbal learning in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society* 2010; 16(3):506-516. *(please see Appendix B)*

Summary:

Following mild traumatic brain injury (TBI), a percentage of individuals report chronic memory and attention difficulties. Traditional neuropsychological assessments often fail to find evidence for such complaints. We hypothesized that mild TBI patient may in fact experience subtle cognitive deficits that reflect diminished initial learning ability that can be explained by changes in cerebral white matter microstructure. We examined trial by trial learning on the the California Verbal Learning Test II. Overall, patients with mild TBI showed intact total learning (at the end of 5 trials) but impaired learning at Trial 1. Furthermore, the imaging data was used as a correlate. Performance on Trial 1 was associated with reduced fractional anisotropy in the uncinate fasciculus and the superior longitudinal fasciculus providing an anatomical correlate for the cognitive findings. Mild TBI patients were not impaired relative to control participants on total learning or memory composite variables. Performance on the initial learning trial was not related to any psychological variables including mood. We concluded that patients with mild TBI demonstrate diminished initial learning ability that is not often interpreted in standard neuropsychological assessment. *Specific methodological details and findings are present in the appendix.*

In summary, we have accomplished each task within our scope of work and have developed new methods that can be applied to the data. Our subject recruitment is on-task. We hope to increase subject recruitment in the coming year to allow more focus on the data analysis. We look forward to the opportunity of continuing this work in the year ahead.

Please note that this published manuscript in part addresses Aim 4

Experimental Data Analysis Conducted to Date –Manuscripts in Preparation or Under Review

Geary EK, Kraus MF, Pliskin NH, Rubin L, Little DM. Passive learning strategies in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society*.

Summary:

That learning and memory deficits persist many years following mild traumatic brain injury (TBI) is controversial due to inconsistent objective evidence supporting subjective complaints. Our prior work demonstrated significant reductions in performance on the initial trial of a verbal learning task in well-motivated mild TBI participants relative to demographically matched controls. In our original work, we speculated that differences in strategy use could explain the initial verbal learning discrepancies. The current study serves to test this hypothesis by examining strategy use on the California Verbal Learning Test-Second Edition. Our present findings support the primary hypothesis that mild TBI participants under-utilize semantic clustering strategies relative to control participants. Although there were no differences in strategy use for the initial two trials, mild TBI participants showed reductions in semantic clusters on the third and subsequent trials. We posit that the chronic learning and memory difficulties reported by some mild TBI patients are related to this reduced utilization of internally-driven strategies that facilitate learning and enhance recall. Given that strategy training has demonstrated improvements in learning and memory in educational and occupational settings, we offer that these findings have translational value in offering an additional approach to remediation. These data are described in Figure 4. *The manuscript is currently being revised to be resubmitted for publication to JINS and is included as an appendix.*

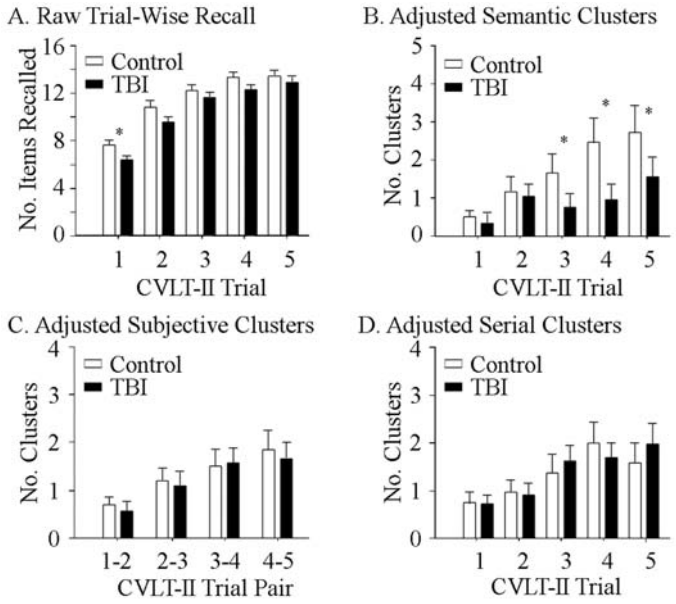

Figure 4. CVLT-II raw recall and cluster analyses for manuscript described to the left.

<u>Please note that this manuscript in part addresses Aim 4</u>

Geary EK, Moynihan M, Kraus MF, Little DM. Cortical and cerebellar atrophy in chronic mild traumatic brain injury. *To be submitted, Brain Injury*.

Summary:

Following traumatic brain injury (TBI), diffuse cerebral atrophy and focal injury are often evident on magnetic resonance imaging (MRI). While individuals who suffer the most severe injury often exhibit readily observable atrophy using conventional imaging methods, individuals with mild TBI may also evidence changes in gray and white matter integrity several years after injury (Kraus et al, 2007; Lo et al). Voxel-based morphometry (VBM) is an automated technique used in neuroimaging analyses that detects atrophy by measuring differences between groups in local brain tissue concentration. Rather than utilizing a limited number of a priori specified

regions of interest, VBM involves comprehensive whole-brain analysis. After realigning MRI images into normalized space, voxels are segmented and classified as gray matter, white matter or cerebrospinal fluid and then smoothed to calculate tissue composition maps (Good et al, 2001; Bandettini, 2009). While changes in gray and white matter have been identified in hypothesis-driven region specific analyses, analyses of whole brain gray and white matter voxel by voxel volume differences in TBI are scarce. Further, these few studies in TBI consisted of relatively small samples collapsed across the range of injury severity. In the present study, we utilized voxel-based morphometry to conduct whole brain group comparisons between control subjects and those with a history of mild TBI subjects to determine the presence of differences in gray and white matter volume between groups. In areas that demonstrated atrophy, we then attempted to determine the relationship of brain volume to cognitive performance.

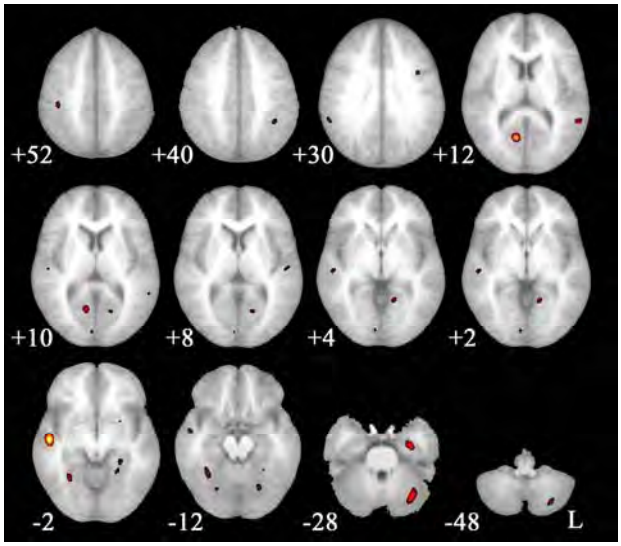

Figure 5. Regions showing increased atrophy in TBI as compared to demographically matched healthy controls.

Methods: A total of 69 patients with a history of TBI were identified based upon American Congress of Rehabilitation Medicine guidelines. These guidelines include any period of loss of consciousness (LOC) or alternation of mental status, anterograde or retrograde amnesia for the acute injury period and/or any focal neurological deficit. Of these 69 TBI patients, 43 met criteria(4-7) for classification as mild TBI (LOC less than 30 minutes, PTA less than 1 hour) Of the 43 mild TBI, 14 reported a history of multiple mild TBI (10 had a history of 2 mild TBI, 4 had a history of 3 mild TBI).

For the image analysis, we used the methods described by Ashburner and Friston (2000, 2001). The normalized images are then segmented into GM, WM, air, and CSF. MRI images were analyzed with SPM5 (Wellcome Department of Neurology, London, UK). SPM5 was run using MATLAB 7.0.1 (Mathworks, Natick, Massachusetts, USA). Data for each subject was aligned in the axial, coronal, and sagittal plane. Images were then spatially normalized to the MNI T1 template and smoothed using an 8mm full-width at half maximum Gaussian kernel. The final preprocessing step was segmentation into gray matter, white matter, and cerebrospinal fluid at a 1x1x1mm^3 voxel size.

Findings: Patients with a history of mild TBI showed atrophy in the right and left superior intraparietal sulci, left frontal eye fields, posterior cinguate, medial temporal gyri, superior temporal gyri, inferior temporal gyri, and bilaterally in the cerebellum. Of greatest clinical relevance (correlation to behavior) was marked atrophy of the cerebellum. Given the extensive network of feedback and feedforward networks that rely upon the cerebellum this finding is of great significance and novel in TBI. The regions identified as showing atrophy in as little as one year post-injury in mild TBI are shown in Figure 5. This manuscript is being revised and will be submitted to Brain Injury.

<u>Please note that although this specific analysis was not included in the Aims the preliminary analyses conducted led us to investigate structural alterations in terms of atrophy. These results have led us to also examine the integrity of the cerebellar fiber tracts in more detail.</u>

Little DM, Kashyap S, Ravich Z, Geary EK. Diffusion tensor imaging markers of brain stem in TBI.

Summary:

Experimental animal models of traumatic brain injury (TBI) demonstrate that the upper brainstem is particularly susceptible to mechanical strain from brain movement in acceleration/deceleration injuries. Similarly, human studies using patients with a history of moderate-severe TBI have demonstrated that the presence of lesions within the brainstem is associated with the poorest outcomes. This finding has led to the speculation that the presence of acute post-concussive symptoms (PCS) (e.g., nausea/vomiting, dizziness, visual disturbance) in patients with a history of TBI likely reflects sub-threshold injury to brainstem structures and tracts. While the role of the brainstem is well established in moderate to severe TBI, the involvement of the brainstem in milder injury is less well understood. In the current study, we hypothesized that acute PCS shared across all severities of TBI reflect brainstem disruption. Thus, we undertook an examination of integrity of brainstem fiber tracts and key brainstem structures which are purported to underlie mood and behavioral complaints following closed head injury.

High resolution diffusion tensor imaging (DTI) was carried out in patients with a history of a single closed-head injury (n=15 mild TBI, 15 moderate severe TBI, 15 healthy uninjured controls) who were at least 6 months from injury. Fractional anisotropy (FA) was extracted from six white matter fiber tract targets including the cerebral peduncle, pontine crossing fibers, superior cerebellar peduncle, medial lemniscus, cortico-spinal tracts, and middle cerebellar peduncle. Additionally, regions of interest were placed in the substantia nigra and red nucleus. The locations of the regions of interest and methods for placement are included in Figure 6

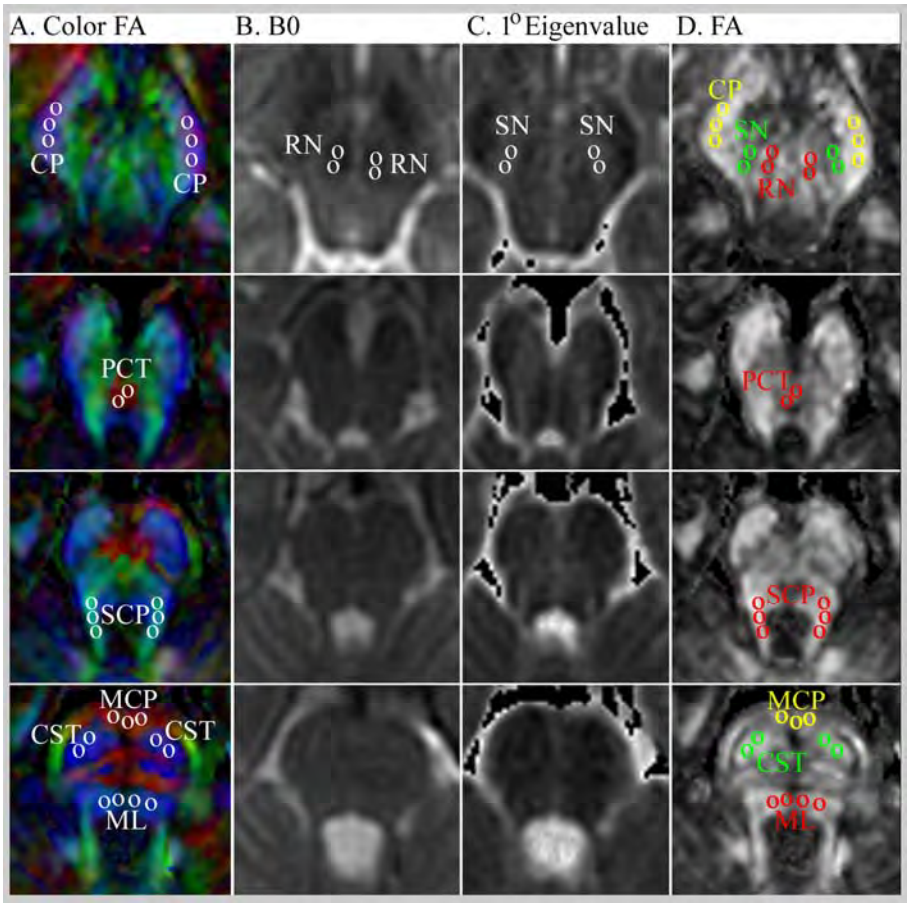

Figure 6. Placement of the regions of interest for brainstem analyses.

Patients with a history of moderate to severe TBI showed reduced FA in the, pontine crossing fibers, medial lemniscus, cortico-spinal tracts, and middle cerebellar peduncle. Additionally, reduced FA was also observed in the substantia nigra and red nucleus. In mild TBI, the same regions were also different than controls with the exception of the middle cerebellar peduncle and red nucleus. Of these, integrity of the substantia nigra, superior cerebellar peduncle, and cerebral peduncles were associated with depressive and post-concussive symptoms. These findings provide initial evidence that the brainstem may represent a site of shared pathology across TBI of all severities. These data are presented in Figure 7.

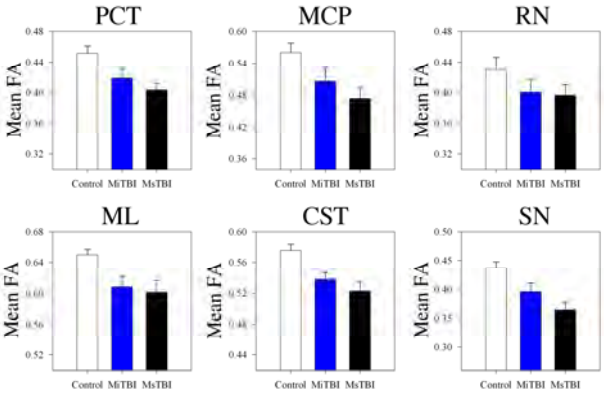

Figure 7. Results of brainstem analysis using diffusion tensor imaging data in controls, mild TBI and moderate to severe TBI for each region of interest which showed a significant effect of head injury ($p<0.05$)

These data directly address Aim 2 from the proposed research.

Little DM, Kashyap S, Ravich Z, Geary EK. Diffusion tensor imaging markers of basal ganglia injury in TBI.

Summary:

Across all severities of traumatic brain injury (TBI), deficits in mood and emotion regulation are commonly reported. In moderate to severe brain injury, the incidence of depression has been found to be as high as 77% (Varney et al., 1987). However, although lower than moderate to severe injury, even milder TBI show increased rates of emotional and cognitive problems (Kraus et al., 2005). It is unknown whether this increased incidence is due to alterations in metabolism, structural damage to key regions, or other factors. The objective of the current study was to assess whether damage to key subcortical structures which are known to underlie neurobehavioral function in other populations is associated with depressive symptoms in chronic TBI. For the present study we focus on structural integrity of the basal ganglia which are implicated in mood regulation and higher order function. In TBI, although the basal ganglia are less likely to sustain damage from a direct impact or contusion they are known to be susceptible to diffuse axonal injury which results from shear and strain forces in TBI with lesions commonly being observed in the putamen. In the current study we hypothesized that damage to the basal ganglia, specifically the caudate and putamen, are associated with increased depressive symptoms following all any severity of TBI.

Methods: High resolution diffusion tensor imaging (DTI) was carried out in patients with a history of a single closed-head injury (n=18 mild TBI and 18 moderate TBI) and 18 healthy uninjured controls. The patients were at least 6 months from injury and demographically matched to the controls. Fractional anisotropy (FA) was extracted from the caudate and putamen of the basal ganglia bilaterally. These locations for regions of interest are shown in the right of Figure 6.

Results: All patients with a history of TBI showed reduced FA in both the caudate and putamen of the basal ganglia. In mild TBI but not moderate severe, the integrity of the caudate and putamen were associate with an increase in depressive symptoms as determined by the Beck Depression Inventory. Data from significant regions of interest are presented in the left of Figure 6.

Conclusion: This study provides preliminary evidence to suggest that structural alterations in the basal ganglia are associated with increased depressive symptoms in TBI.

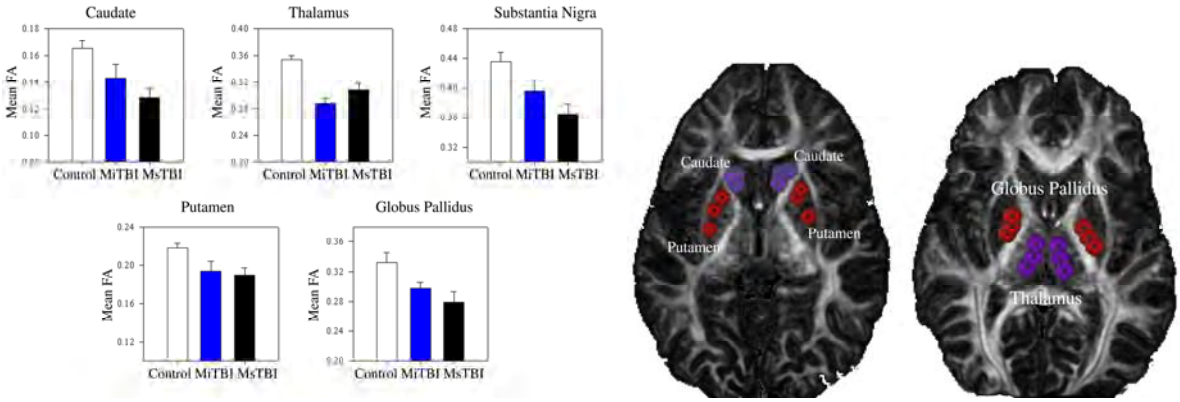

Figure 6. Results from the proposed region of interest analysis evaluating integrity of the basal ganglia in TBI.

These data directly address Aim 2 from the proposed research.

Key Research Accomplishments

1. The thalamus has been identified as a potential biomarker that consistently shows damage across all severities of TBI and correlates with alterations in cognitive function. This finding was published in Neurology and therefore has been peer reviewed.
2. Although cognitive alterations in mild TBI are generally thought to resolve with time we demonstrated that there are subtle but significant alterations that maintain over time. We believe that these subtle alterations result in the discrepancy between verified cognitive impairment (via neuropsychological testing) and self-report. This finding was published in JINS and therefore has been peer reviewed.
3. There is significant atrophy associated with even a single mild TBI. This would suggest that the pathological processes associated with injury do not cease at the time of the injury but continue. We believe that this may be associated with the increased risk of dementia following head injury. It is important to note that this data has not yet been peer reviewed and is thus considered preliminary.
4. We have preliminary data to suggest that there is significant damage to the brainstem in mild TBI and that this damage directly relates to sustained post-concussive symptoms. However, as with the above, it is important to note that these findings have not yet been peer reviewed and should be considered preliminary.

Reportable Outcomes

1. **Publication of two data-driven manuscripts based upon data collected for this grant.**

Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, Pliskin N, Gorelick PB. Thalamic integrity underlies executive dysfunction: Evidence from Traumatic Brain Injury. *Neurology* 2010; 74: 558-564 (PMID: 20089945).

Geary EK, Kraus MF, Pliskin NH, **Little DM**. Impairments in verbal learning in chronic mild traumatic brain injury. *Journal of the International Neuropsychological Society* 2010; 16(3):506-516.

2. Acceptance of 7 abstracts for the presentation of the research supported by this grant.

Siroko M, Moynihan M, Geary EK, **Little DM**. Effects of head trauma on brainstem fiber integrity.Program No. 659.21. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. Online.

Schulze E, Geary EK, Abraham S, **Little DM**. Effects of diffuse axonal injury on the basal ganglia in chronic TBI. Program No. 659.26. 2010 Neuroscience Meeting Planner. San Diego, CA: Society for Neuroscience, 2010. Online.

Geary EK, Kraus MF, **Little DM**. Verbal learning impairments in mild traumatic brain injury. International Brain Injury Association, Washington DC, March 2010.

Little DM, Kraus MF, Wojtowicz S, Siroko M, Alexander A, Sweeney JA. Prefrontal-thalamocortical circuitry dysfunction in traumatic brain injury. Program No. 541.8 R11. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

Moynihan MP, Geary EK, Kraus MF, **Little DM**. Consequences of traumatic brain injury: Neurobehavioral correlates of cerebral atrophy. Program No. 641.8 S12. 2009 Neuroscience Meeting Planner. Chicago, IL: Society for Neuroscience, 2009. Online.

Little DM, Kraus MF, Zhou XJ, Joseph J, Susmaras T, Geary EK, Pliskin N, Gorelick P. High-resolution diffusion tensor imaging of thalamic projection fibers in TBI. International Neurotrauma Society Meeting, Santa Barbara, CA 2009.

Little DM, Kraus MF, Joseph J, Geary EK, Susmaras T, Zhou XJ, Gorelick PB. Thalamic projection fibers and cognitive impairment following traumatic brain injury. Department of Defense Military Health Research Forum. Kansas City, MO 2009.

3. **Eleven invited presentations or colloquia on the topics and data supported by this grant. These include a Society for Neuroscience Presidential Symposia, the Annual World Congress of IBMISPS at Uniformed Services University of Health Sciences and workshop invitations including as part of the mild TBI Diagnostics Workshop funded by the DoD, NIH, and VA in St. Pete Flordia.**

The Role of Diffusion Tensor Imaging in Diagnosis of Mild TBI: Diagnostic Tool or Just Another Pretty Picture?
Neuroscience of Brain Injury: Research Informing Medical and Legal Practice, California Brain Injury Association, Napa CA (November 2010)

Hidden in Plain Sight: Injury and Damage Characterization following Concussion.
Claremont-Mudd-Scripps Neuroscience Lecture Series, Claremont CA (November 2010)

High Resolution Diffusion Imaging of Mild TBI
University of Illinois Behavioral Neurosciences Seminar Series, Chicago IL (October 2010)

Neuroimaging and Neurophysiology of Mild Traumatic Brain Injury
Grand Rounds, North Chicago Veterans Affairs Medical Center, North Chicago, IL (July 2010)

Magnetic Resonance Diffusion Tensor Imaging for the Assessment of Diffuse Axonal Injury in TBI. 7th Annual World Congress of IBMISPS on Brain, Spinal Cord Mapping and Image Guided Therapy, Uniformed Services University of Health Sciences, Bethesda MD (May 2010).

Sensitivity of Neuropsychological Assessment in Mild TBI
Department of Psychology, University of Oregon (May 2010)

Imaging Mild TBI: What's the point?
Teaching Research Institute of Oregon; Eugene OR (May 2010)

Imaging in TBI: The Search for a Central Mechanism of Injury
Presidential Symposium on Traumatic Brain Injury, Chicago Chapter, Society for Neuroscience Annual Meeting (March 2010).

Central Mechanisms of Injury in Mild Traumatic Brain Injury
Medical Grand Rounds, Rosalind Franklin University (February 2010).

Neuroimaging Mild Traumatic Brain Injury
Thorek Hospital Grand Rounds; Chicago, IL (January 2010).

Neurophysiology of Traumatic Brain Injury
University of Illinois Department of Ophthalmology and Visual Sciences Visual Neuroscience Grand Rounds (November 2009).

From Chronic to Acute and Civilian to Military – Use of Imaging Biomarkers of Mild Injury to Identify Behavioral Assessment Measures.
mTBI Diagnostics Workshop, St. Pete FL (August 2010)

4. **Grants applied for and/or funded.**

"Neuroimaging and Neurophysiology in mild TBI"
PI: Deborah M. Little PhD
Duration: 8/1/2011-7/31/2015
Effort: 6PM (based upon a 4/8ths VA appointment)
Sponsor: Department of Veterans Affairs
Overview: The purpose of the grant is to investigate the effects of blast+ mild TBI on thalamic and brain stem fiber integrity and function using a combination of neuropsychological testing, high field MRI, and tests of oculomotor function. Preliminary data obtained from the current award was used to apply for this funding. It is important to note that the pending application (it will start in August when this grant has completed) was used. It should also be noted that the funded grant has an absolute focus on TBI sustained in theater and takes the current application and advances it by testing the theory that damage to the thalamus and brain stem result in both structural and physiological alterations.

Conclusion

The results of the work accomplished in year 2 are significant. First, we have provided data to suggest that there is a central mechanism of cognitive impairment in TBI. If validated by other laboratories this has the potential to change treatment approaches and assessment of treatment validity. Beyond the publication of the work in the thalamus we have also published work that challenges current approaches to neuropsychological testing. We have included a pdf copy of

both manuscripts at the end of this report. Finally, some of the data collected in support of this grant was included as preliminary data for a VA RR and D Merit Award application. This is significant because I have just received a notice of award on this grant. The focus of the grant is on validating the methods established in civilian acceleration-deceleration TBI from the current award in blast+ OIF/OEF Veterans. We expect that with the completion of data collection in Year 3 at least 4 additional manuscripts will be submitted which will further push this field forward. Additionally, it is important to note that for Aim 3 of the proposed research, analyses are on-going but due to variability in the data additional power is needed. As such, we do not expect to address Aim 3 until data collection is complete.

References

None.

Appendix 1

Thalamic integrity underlies executive dysfunction in traumatic brain injury

D.M. Little, PhD
M.F. Kraus, MD
J. Joseph, BS
E.K. Geary, PhD
T. Susmaras, BA
X.J. Zhou, PhD
N. Pliskin, PhD
P.B. Gorelick, MD, MPH

Address correspondence and reprint requests to Dr. D.M. Little, 1645 West Jackson Suite 400, Chicago, IL 60612
little@uic.edu

ABSTRACT

Objective: To quantify the effects of traumatic brain injury on integrity of thalamocortical projection fibers and to evaluate whether damage to these fibers accounts for impairments in executive function in chronic traumatic brain injury.

Methods: High-resolution (voxel size: 0.78 mm × 0.78 mm × 3 mm^3) diffusion tensor MRI of the thalamus was conducted on 24 patients with a history of single, closed-head traumatic brain injury (TBI) (12 each of mild TBI and moderate to severe TBI) and 12 age- and education-matched controls. Detailed neuropsychological testing with an emphasis on executive function was also conducted. Fractional anisotropy was extracted from 12 regions of interest in cortical and corpus callosum structures and 7 subcortical regions of interest (anterior, ventral anterior, ventral lateral, dorsomedial, ventral posterior lateral, ventral posterior medial, and pulvinar thalamic nuclei).

Results: Relative to controls, patients with a history of brain injury showed reductions in fractional anisotropy in both the anterior and posterior corona radiata, forceps major, the body of the corpus callosum, and fibers identified from seed voxels in the anterior and ventral anterior thalamic nuclei. Fractional anisotropy from cortico-cortico and corpus callosum regions of interest did not account for significant variance in neuropsychological function. However, fractional anisotropy from the thalamic seed voxels did account for variance in executive function, attention, and memory.

Conclusions: The data provide preliminary evidence that traumatic brain injury and resulting diffuse axonal injury results in damage to the thalamic projection fibers and is of clinical relevance to cognition. *Neurology*® 2010;74:558–564

GLOSSARY

ACR = anterior corona radiata; **AN** = anterior thalamic nucleus; **bCC** = body of the corpus callosum; **CST** = cortical-spinal tract; **DAI** = diffuse axonal injury; **DM** = dorsomedial nucleus; **DTI** = diffusion tensor imaging; **FA** = fractional anisotropy; **fMaj** = forceps major; **fMin** = forceps minor; **FOV** = field of view; **FSE** = fast spin echo; **gCC** = genu of the corpus callosum; **IC** = internal capsule; **IFOF** = inferior frontal occipital fasciculus; **LOC** = loss of consciousness; **miTBI** = mild TBI; **msTBI** = moderate to severe TBI; **NEX** = number of excitations; **PCR** = posterior corona radiata; **PTA** = posttraumatic amnesia; **PU** = pulvinar; **ROI** = region of interest; **sCC** = splenium of the corpus callosum; **SLF** = superior longitudinal fasciculus; **SS** = sagittal stratum; **TBI** = traumatic brain injury; **TE** = echo time; **TR** = repetition time; **VA** = ventral anterior thalamic nucleus; **VL** = ventral lateral thalamic nucleus; **VPL** = ventral posterior lateral nucleus; **VPM** = ventral posterior medial nucleus.

Traumatic brain injury (TBI) is a serious public health problem with a high incidence[1-3] which can result in structural damage to the cerebrum including contusions, edema, and diffuse axonal injury (DAI).[4] DAI has been demonstrated in all stages and severities[5-7] and is often the only significant pathology in milder injury.[6,8-15] The variable nature of injury mechanism, severity, lesion presence, and location makes the identification and definition of the key cere-

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From the Departments of Neurology (D.M.L., M.F.K., J.J., E.K.G., T.S., P.B.G.), Anatomy (D.M.L.), Ophthalmology (D.M.L.), Psychiatry (M.F.K., E.K.G., N.P.), Neurosurgery and Radiology (X.J.Z.), and Bioengineering (X.J.Z.), and from the Center for Stroke Research (D.M.L., J.J., E.K.G., T.S., P.B.G.), Center for Cognitive Medicine (D.M.L., M.F.K., N.P.), and MR Research (X.J.Z.), The University of Illinois Medical Center at Chicago, Chicago.

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bral mechanisms which underlie behavioral impairments challenging. Behaviorally, patients with a history of TBI commonly have deficits in cognition, behavior, and mood that load heavily on the executive or frontal lobe functions.[16-20] However, the relationship between measures of frontal lobe structure and shearing within frontal lobe white matter tracts and cognition are generally weak.[7,19,21] This weak relationship between frontal structure and function, coupled with the finding that DAI not only affects local function but can also disrupt critical cortical-subcortical pathways,[22,23] led us to the general hypothesis that damage to cortical-subcortical fibers projecting to and from the thalamus contribute to chronic impairment in cognition and behavior. This hypothesis is supported by the report that thalamic volume is related to 2-year outcome.[24] We tested the hypothesis that damage to thalamic projection fibers underlies executive function impairments using high-resolution diffusion tensor imaging of the thalamus (DTI) in a group of healthy controls and in 2 groups of patients who had sustained a closed-head brain injury.

METHODS

Standard protocol approvals, registrations, and patient consents. The research was conducted in compliance with both institutional (University of Illinois at Chicago) and federal (Department of the Army) human subjects guidelines using standards consistent with the declaration of Helsinki. All subjects provided prospective, written, informed consent.

Participant characteristics. A total of 24 patients with a history of a single, closed-head type TBI were recruited via advertisements in local newspapers (no patients were recruited from an active clinical practice) and were screened and consented in the order they responded to advertisements. Inclusion criteria for patients and controls included age at study (18–50 years of age included), education (at least 1 year of high school), negative history (prior to TBI) for psychiatric illness, and English as a native language. For patients with TBI, age at injury was required to be after age 16 and at least 12 months prior to study. Patients were classified as having had a mild TBI (miTBI) if they reported either no loss of consciousness (LOC) or a LOC less than 30 minutes and posttraumatic amnesia (PTA) for less than 24 hours. Patients were classified as moderate to severe TBI (msTBI) if they experienced LOC greater than 30 minutes, PTA greater than 24 hours, or a positive MRI or CT study for contusion, edema, or ischemia at the time of injury. Detailed clinical assessments were carried out (M.F.K.) to establish injury severity and extract specific injury variables including mechanism of injury, presence and duration of LOC, neurologic examination, presence of posttraumatic headache, and associated injuries at the time of TBI. See table e-1 on the *Neurology*® Web site at www.neurology.org for details. Estimates of PTA and LOC are presented as the nature and time from injury makes accurate estimates difficult. Subjects were excluded if they were taking any medications used to enhance cognitive function, had significant depressive symptoms, had current or past litigation related to the injury, or had failure on tests of effort and symptom validity. All but 2 of the patients with TBI had returned to work or school following the injury. Of the 2, 1 was unable to return to work and the other dropped out of college. The gross majority of subjects reported a level of function less than prior to the injury (20 of 24) even though more than 14 returned to the same job or matriculated to the next stage of schooling. Of the 24 patients with TBI, all but 3 reported some degree of sustained problems with cognition or sustained alteration in cognitive function at the time of testing. In terms of alterations in behavior, 12 of the 24 reported sustained alterations in behavior following the TBI.

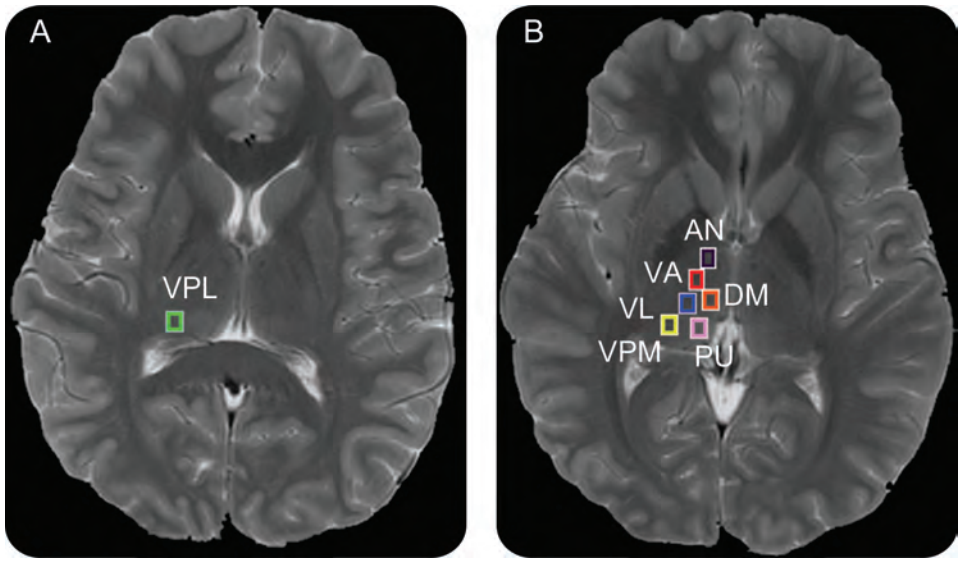
The groups were matched on age and education, with controls reporting 15 years of formal education (mean = 15.4, SEM = 0.6) and age at study of 31 years (mean = 30.8, SEM = 3.04); miTBI reporting16 years of formal education (mean = 16.4, SEM = 0.36) and age at study of 31 years (mean = 31.2, SEM = 2.71); and msTBI reporting 16 years of formal education (mean = 16.1, SEM = 0.60) and age at study of 33 years (mean = 33.3, SEM = 3.20). The miTBI and msTBI were roughly matched for age at injury (miTBI: mean = 27.2 years of age, SEM = 2.4; msTBI: mean = 25.3 years of age, SEM = 2.9). All 3 groups were matched on estimates of premorbid IQ (controls: mean = 112.4, SEM = 3.55; miTBI: mean = 111.2, SEM = 2.78; msTBI: mean = 111.7, SEM = 1.6).

Statistical analyses. Neuropsychological test scores were analyzed using a one-way analysis of variance with group membership (controls, miTBI, msTBI) as the between-subjects factor and were corrected for multiple comparisons using the least significant difference post hoc tests. The primary measures of interest were 3 scores which were each a composite of those individual test results which loaded preferentially on executive, memory, and attention domains. Group differences on individual neuropsychological tests were corrected for multiple comparisons using the Bonferroni correction. The primary analyses carried out on the dependent measures extracted from the DTI data were a one-way mixed design analysis of variance with group membership (controls, miTBI, and msTBI) as the between-subjects factor. The primary dependent measure was fractional anisotropy (FA). Data were confirmed to have a normal distribution using the Kolmogorov-Smirnov test. To examine the relative contributions of thalamic and cortical (to include cortico-cortico and corpus callosum white matter) regions of interest, both bivariate correlations and stepwise linear regressions were used.

Neuropsychological testing. Subjects completed a neuropsychological battery comprised of tests known to be sensitive to the cognitive deficits associated with TBI, with a focus on tests of executive function, attention, memory, and processing speed. Additional measures were included to assist in the estimation of premorbid function and to assess effort. Tests and selected scores from the tests are included in table e-2. These test scores were converted to standardized *z* scores (based upon control means) and combined to create 3 cognitive domains (executive, attention, memory).

Image acquisition. In order to reliably perform the FA analysis and fiber tracking in the thalamus, we used a customized high-resolution DTI protocol which relied on a single-shot EPI acquisition[25] together with parallel imaging using an 8-channel phased-array head coil on a GE 3.0 T Signal HDx scanner (Gen-

Figure 1 Thalamic nuclei



Seed regions for the ventral posterior lateral nucleus (VPL) (green), anterior thalamic nucleus (AN) (purple), ventral anterior thalamic nucleus (VA) (red), dorsomedial nucleus (DM) (orange), ventral lateral thalamic nucleus (VL) (blue), ventral posterior medial nucleus (VPM) (yellow), and pulvinar (PU) (pink) overlaid on the T2-weighted images.

eral Electric Healthcare, Milwaukee, WI). The imaging parameters included repetition time (TR)/echo time (TE) = 5,000/64 msec, b = 0,1000 s/mm^2, diffusion directions = 27, field of view (FOV) = 20 × 20 cm^2, matrix = 256 × 256, slice thickness/gap = 3/0 mm, slices = 7, number of excitations (NEX) = 8, and acceleration factor = 2. In order to visualize the thalamus and differentiate the thalamus from surrounding structures, a set of 2D T2-weighted images were acquired (fast spin echo [FSE], axial, TR/TE = 4,000/80 msec, ETL = 8, matrix = 512 × 256, FOV = 20 × 20 cm^2, slices = 7, slice thickness/gap = 3/0 mm). To visualize the dorsomedial nucleus, 3-dimensional inversion recovery spoiled gradient recalled echo (3DIRpSPGR) images were acquired (TR/inversion time/TE = 13.8/600/2.7 msec, flip angle = 25°, matrix = 512 × 192, FOV = 22 × 16 cm^2, slices = 120, slice thickness = 1.5 mm, NEX = 1, bandwidth = ±15.6 kHz).

Diffusion tensor imaging and analysis. DTI is a type of diffusion-weighted imaging that allows the assessment and visualization of large white matter fibers on a millimeter-level multidimensional scale. DTI takes advantage of the diffusivity of water and the restrictions imposed on the diffusion of water by white matter fiber tracts. When fiber tracts are dense the restriction imposed by their density leads to directionally dependent or anisotropic diffusion with the shape of water diffusion occurring preferentially along those tracts. When there is less organization or a lack of aligned and organized fiber structures (i.e., gray matter, CSF, axonal loss, or demyelination) the shape of water diffusion will be more isotropic. Commonly, the degree of alignment and anisotropy is calculated as the FA. FA values range from 0 to 1, where 0 represents isotropic diffusion and 1 represents anisotropic diffusion.

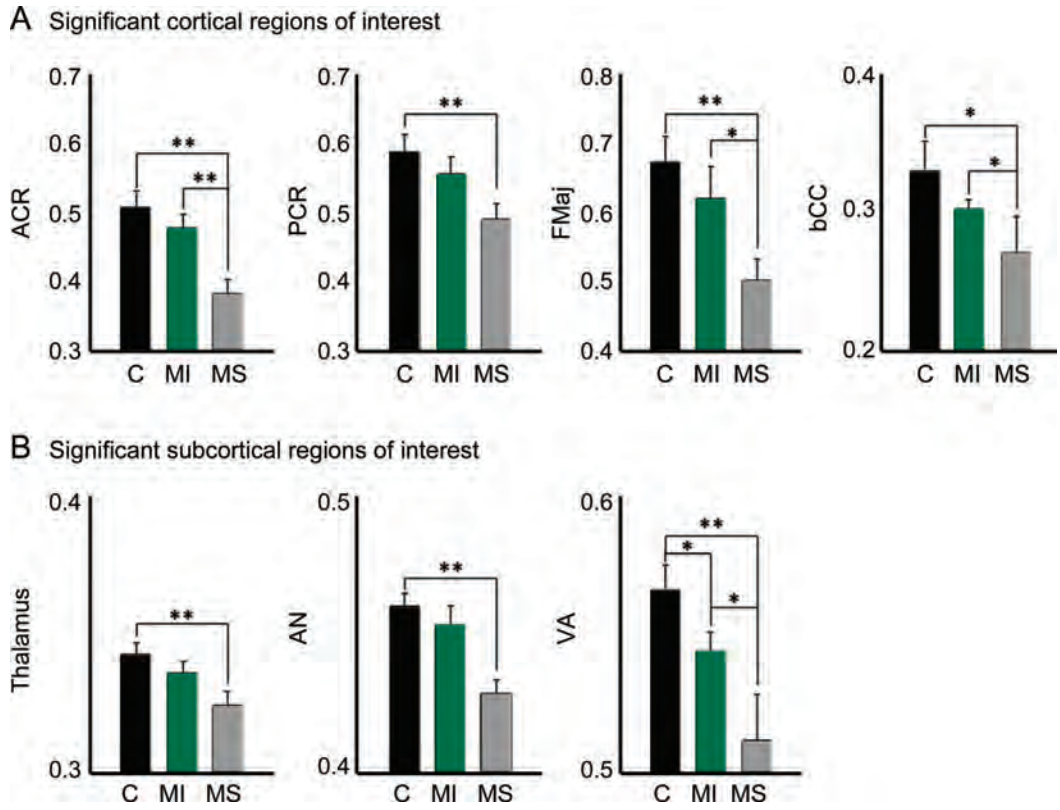
In the present study, the diffusion images were reconstructed and FA calculated using DTI Studio.[26] For each slice, the set of 28 DTI images were examined for image quality. Head movement was required to be within 1 voxel across the image acquisition. Because noise can introduce bias in estimates of the eigenvalues and decrease the signal-to-noise ratio, a background noise level of 125 (MR units) was applied prior to calculation of pixel-wise FA, eigenvectors, and eigenvalues. All region of interest (ROI) analyses were carried out on each individual in original image space.

Effects of trauma on cerebral white matter. To assess the effects of trauma on DTI, 3 analyses were applied. Gross measures of whole brain FA and thalamic FA were extracted. For the whole brain mask, each voxel with a FA greater than 0.2 was included (ensuring only white matter in the calculations). Second, specific ROI were drawn on corpus callosum and cortico-cortico white matter tracts, which have been previously implicated in head injury.[7] These "cortical" ROIs were placed on the cortical-spinal tract (CST), anterior corona radiata (ACR), posterior corona radiata (PCR), forceps minor (fMin) and forceps major (fMaj), sagittal stratum (SS), internal capsule (IC), inferior frontal occipital fasciculus (IFOF), superior longitudinal fasciculus (SLF), and in the genu (gCC), body (bCC), and splenium (sCC) of the corpus callosum. Separate ROIs were placed in the left and right hemisphere where appropriate. Details on placement can be found in figure e-1.

Finally, fiber tracking was used to assess damage to the fibers projecting from the thalamus. Seed voxels (small ROIs) were placed in 7 thalamic regions (shown in figure 1) including the anterior thalamic nucleus (AN), ventral anterior thalamic nucleus (VA), ventral lateral thalamic nucleus (VL), dorsomedial nucleus (DM), ventral posterior lateral nucleus (VPL), ventral posterior medial nucleus (VPM), and pulvinar (PU). The purpose of these seed voxels is to identify all fiber tracts which run through this region. FA can then be extracted from these fibers identified by the seed voxels and fiber tracking from these seeds. Interrater reliability was greater than 0.94 for placement of AN, VA, DM, VL, and PU seed voxels. Interrater reliability was 0.85 for VPL and VPM. Specific details and rules for placement are included in appendix e-1 and figure e-2.

RESULTS Behaviorally, patients with a history of TBI performed worse on measures of executive func-

Figure 2 Average cortical and subcortical fractional anisotropy (FA)



Mean FA extracted from the anterior corona radiata (ACR), posterior corona radiata (PCR), forceps major (fMaj), and body of the corpus callosum (body of the corpus callosum) as well as from the thalamus and from fibers identified from seed regions in the anterior thalamic nucleus (AN) and ventral anterior thalamic nucleus (VA). Significant post hoc comparisons between groups are indicated (*$p < 0.05$; **$p < 0.01$). Cortical in this figure refers to regions of interest that include cortico-cortico tracts and regions in the corpus callosum.

tion relative to controls [$F(2,36) = 5.15$, $p = 0.011$, $\eta^2 = 0.26$]. Although there were trends for reduced attention and memory performance in TBI, neither of these comparisons reached significance. These findings are consistent with previous work from our group and the literature in general.[7,27-29] A detailed list of performance for each subject group on each test can be found in table e-2.

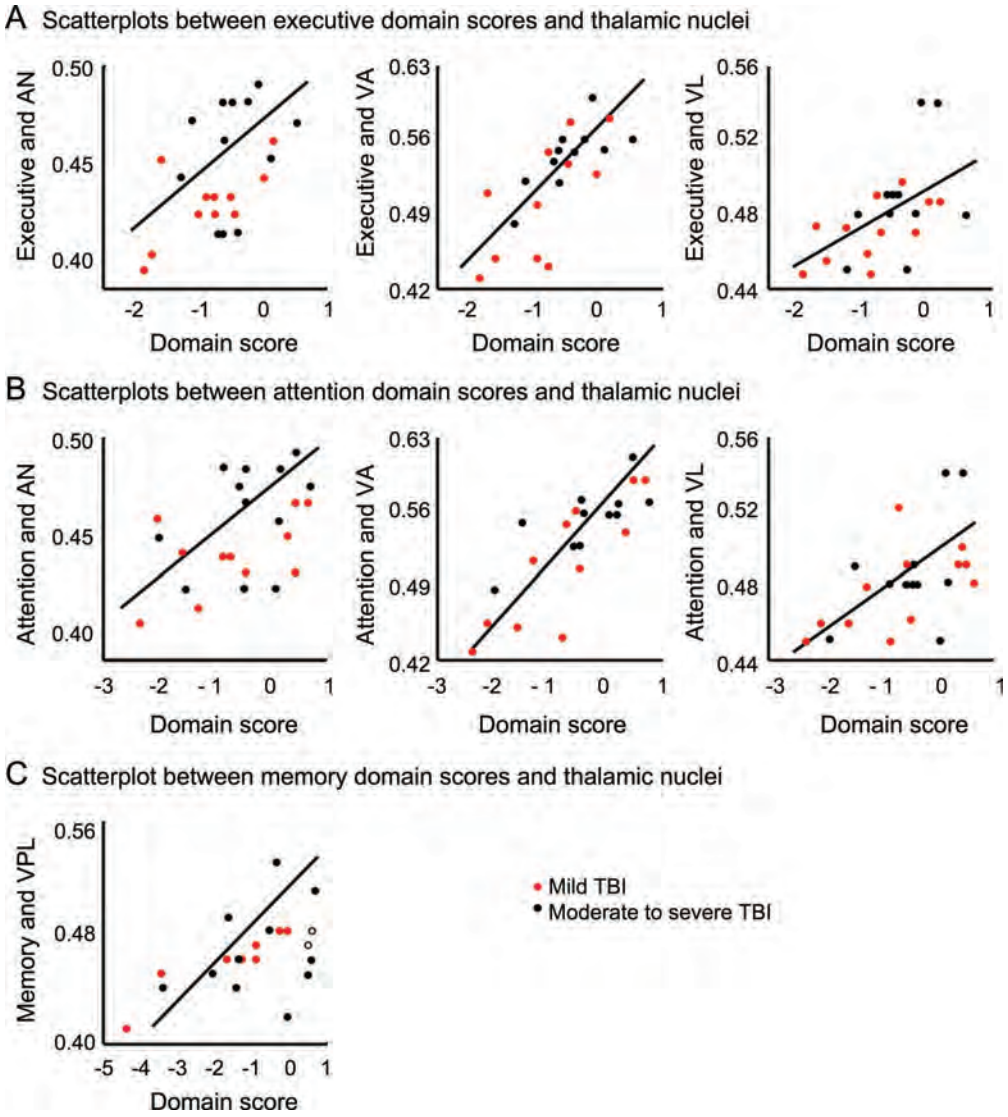
There was an overall effect of subject group (controls, miTBI, msTBI) on FA in the ACR [$F(2,36) = 9.71$, $p < 0.001$, $\eta^2 = 0.0.37$], PCR [$F(2,36) = 3.91$, $p = 0.030$, $\eta^2 = 0.19$], fMaj [$F(2,36) = 5.07$, $p = 0.012$, $\eta^2 = 0.23$], and bCC [$F(2,36) = 4.002$, $p = 0.028$, $\eta^2 = 0.20$], with the greatest differences between controls and those with more severe injury (msTBI; see figure 2A). The patients did not differ from controls in the remaining cortical ROIs (see table e-3 for additional details). Nor did they differ in whole brain FA. There was an overall effect of subject group on thalamic FA [$F(2,36) = 5.40$, $p = 0.009$, $\eta^2 = 0.25$] with controls having higher FA in the thalamus than msTBI. Although there was a trend for the miTBI to show reduced FA relative to controls in thalamic FA, the comparison did not reach significance (see table e-3 for additional details).

Comparisons between groups on FA extracted from the seed regions in the thalamic nuclei are presented in figure 2B. There was an effect of subject group only in fibers extracted from the AN [$F(2,36) = 5.82$, $p = 0.007$, $\eta^2 = 0.26$] and VA [$F(2,36) = 4.82$, $p = 0.015$, $\eta^2 = 0.23$] seed voxels. Post hoc comparisons among controls, miTBI, and msTBI are also indicated on figure 2B.

To examine the relationship between cognition and fiber tract integrity, a series of bivariate correlations were conducted. All of the ROIs were included and examined relative to the neuropsychological domain scores for executive function, memory function, and attention. Correlations were conducted for the control and TBI separately so as not to bias the correlation simply because patients show lower FA than controls.

For controls, there was a statistical relationship between the executive domain score and FA of the gCC ($r = 0.685$, $p = 0.014$) as well as FA of fibers identified with the VL seed voxel ($r = 0.586$, $p =$

Figure 3 Relationship between thalamic fractional anisotropy (FA) and cognition



Scatterplots of FA from thalamic seed voxels relative to executive (A), attention (B), and memory (C) domain scores for traumatic brain injury (TBI) patients. Best-fit lines are indicated in black.

0.045). The attention domain scores were also correlated with FA from the VL ($r = 0.668$, $p = 0.018$) and VPL ($r = 0.639$, $p = 0.025$). Memory function in controls was associated with FA in the genu of the gCC ($r = 0.667$, $p = 0.018$) and inferior frontal occipital fasciculus ($r = 0.605$, $p = 0.037$).

Scatterplots of the significant correlations between neuropsychological function and FA for the TBI are presented in figure 3. In the TBI groups, there were no correlations between any cortical or corpus callosum ROIs with executive function, attention, or memory performance. There was a relationship between the attention domain and FA in the gCC ($r = 0.506$, $p = 0.012$). For thalamic seed voxels, executive function was related to FA extracted from seed voxels in the AN ($r = 0.497$, $p = 0.014$), VA ($r = 0.741$, $p < 0.001$), and VL ($r = 0.540$, $p = 0.006$). Similar relationships were also found between the attention domain score and integrity of fibers from the AN ($r = 0.489$, $p = 0.015$), VA ($r = 0.786$, $p < 0.001$), and VL ($r = 0.523$, $p = 0.009$). In contrast, memory function was associated with integrity of VPL fibers ($r = 0.540$, $p = 0.006$). Integrity of DM was not associated with memory function. Correlations between individual neuropsychological tests and ROIs can be found in table e-4.

We also examined the injury variable duration of loss of consciousness relative to FA measures and relative to domain scores. Accurate ranges of LOC were collected for 19 of 24 subjects. The remaining subjects reported LOC but did not have a witness present. Duration of LOC was negatively correlated with the executive domain ($r = -0.460$, $p = 0.048$) and memory domain ($r = -0.500$, $p = 0.029$).

LOC also correlated with FA from the bCC ($r = -0.661$, $p = 0.002$).

Because of a significant amount of shared variance between nuclei, a series of linear regressions were applied to the TBI data with the executive function domain score as the dependent variable. In the first stepwise linear regression, the frontal lobe ROIs including the ACR, fMin, and gCC were entered. This model did not account for the executive domain variance ($r^2 = 0.19$, $p = 0.236$). Because the white matter tracts are not contained within the frontal lobe, we expanded this regression to include any ROIs which have fiber projections to or from the frontal lobes. This model was expanded to include not only the ACR, fMin, and gCC but also the CST, SS, and IFOF. Although this model accounted for more variance than the first model, it still did not reach significance ($r^2 = 0.322$, $p = 0.291$). This same strategy was applied to the fiber projections from the thalamic nuclei. The projections from the AN, VA, VL, and DM were entered into a linear regression with executive function as the dependent measure. This model did account for variance in the executive domain ($r^2 = 0.674$, $p < 0.001$). Within this model, the only unique predictor was FA from the VA seed voxels ($p = 0.001$) with VA accounting for 26% of the unique variance. Duration of LOC was also added into the regression models. Although it accounted for additional variance in the subcortical model ($r^2 = 0.701$, $p < 0.001$), LOC on its own was not a significant unique predictor.

DISCUSSION The present study presents preliminary support for a thalamic hypothesis as a central mechanism of injury and resultant cognitive impairment in TBI. The thalamus, although not located near the skull and therefore less susceptible to direct contusion, is likely differentially sensitive to shear and strain injury because of the corticospinal fibers which extend from the spine to the cortex. Within the thalamus, incoming sensory, motor, and cognitive processing pathways are organized and integrated within distinct nuclei. Following this integration, various thalamic nuclei send diffuse and specific efferent projections to cortical, cerebellar, and subcortical regions. The thalamus is also known to gate and mediate many cognitive, sensory, motor, and behavioral functions and damage to these projection fibers can result in widespread functional impairments.[30,31] Overall, thalamic lesions are associated with a decrease in executive function with larger lesions associated with greater deficits.[32,33] In the case of frontal lobe functions, impairments in executive function could be accounted for by damage to the fiber projections to and from the dorsomedial nucleus or anterior thalamic or ventral anterior thalamic nuclei rather than the frontal lobes per se.

However, because the thalamus is a relay center for the majority of cortical fiber projections, characterization of thalamic damage must include assessments of the integrity not only of thalamus proper but also for fibers entering or exiting the thalamic nuclei. The fiber tracking methods employed here with the spatial resolution provided by the sequences used allow this concern to be addressed. These projection fibers may in fact be even more susceptible to TBI than the thalamus itself because of the sharp turning angles of the cortical-subcortical fibers both as they leave the thalamus and again as they enter the cortex.[22,23]

The present data reaffirm the presence of executive dysfunction in TBI and suggest that executive dysfunction is correlated with cortical-subcortical damage rather than simply due to damage to the cortical frontal lobe structures, cortico-cortico tracts, or corpus callosum alone. This conclusion is supported both by the presence of correlations between executive function and FA in thalamic nuclei and also by the absence of correlations with FA in the measured cortical regions. The data do not, however, identify the location of damage within these fiber tracts. The primary damage to these fibers could occur at the boundary of the thalamus as the fibers exit the thalamus or it could occur at the junction of gray and white matter as the fibers enter the cortex.

Although these conclusions are based upon a relatively small sample (n = 24), the data suggest that thalamic integrity may be a central mechanism in TBI and provide initial evidence that damage to thalamic projection fibers, especially those involved in frontal-thalamic circuitry, is of great importance in understanding executive dysfunction following TBI. Furthermore, the findings support the need for further investigation into the applicability of these measures in other populations which demonstrate executive dysfunction.

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DISCLOSURE

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publishing *Handbook of MRI Pulse Sequences* (Elsevier, 2004); has received speaker honoraria from Beijing Sinorad Medical Technology; is owner of Horizon Medical Physics Services; and receives research support from the NIH [NINDS R01 NS057514 (Co-I), NICHD 1 P50 HD055751–01 (Co-I), NIDA 1R03 DA024975–01 (Co-I), NICHD R01 MH081019 (Co-I), and NIA AG028662 (Co-I)], the US Department of Defense [2008–01645 (Co-I) and Congressionally Directed Medical Research Program PT 075675 (Co-I)], and the University of Illinois Center for Clinical and Translational Sciences. Dr. Pliskin reports no disclosures. Dr. Gorelick serves on adjudication committees for Abbott, Pfizer Inc, POZEN Inc., Savient Pharmaceuticals, Inc., and Takeda Pharmaceutical Company Limited; serves as a consultant for InTouch Health, Bristol-Myers Squibb/Sanofi Pharmaceuticals Partnership, and Eisai Inc.; and serves on steering committees for Bayer-Schering Pharma, Boehringer Ingelheim, and Brainsgate.

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Appendix 2

Journal of the International Neuropsychological Society (2010), Page 1 of 11.

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Verbal learning differences in chronic mild traumatic brain injury

ELIZABETH K. GEARY,[1,2] MARILYN F. KRAUS,[1,3,4] NEIL H. PLISKIN,[1,3,4] AND DEBORAH M. LITTLE[1,2,4,5]

[1]Department of Neurology, The University of Illinois College of Medicine, Chicago, Illinois
[2]Center for Stroke Research, The University of Illinois College of Medicine, Chicago, Illinois
[3]Department of Psychiatry, The University of Illinois College of Medicine, Chicago, Illinois
[4]Center for Cognitive Medicine, The University of Illinois College of Medicine, Chicago, Illinois
[5]Departments of Anatomy, Ophthalmology, and Psychology, The University of Illinois College of Medicine, Chicago, Illinois

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Abstract

Following mild traumatic brain injury (TBI), a percentage of individuals report chronic memory and attention difficulties. Traditional neuropsychological assessments often fail to find evidence for such complaints. We hypothesized that mild TBI patients may, in fact, experience subtle cognitive deficits that reflect diminished initial acquisition that can be explained by changes in cerebral white matter microstructure. In the data presented here, a sample of nonlitigating and gainfully employed mild TBI patients demonstrated statistically significant differences from age and education matched control participants in performance on the first trial of a verbal learning task. Performance on this trial was associated with reduced fractional anisotropy in the uncinate fasciculus and the superior longitudinal fasciculus providing an anatomical correlate for the cognitive findings. Mild TBI patients were not impaired relative to control participants on total learning or memory composite variables. Performance on the first learning trial was not related to any psychological variables including mood. We concluded that patients with mild TBI demonstrate diminished verbal learning that is not often interpreted in standard neuropsychological assessment. (*JINS*, 2010, 1–11.)

Keywords: Concussion, Diffusion tensor imaging, Single trial learning

INTRODUCTION

There is a significant disparity between recent neuroimaging work that detects measurable changes in brain structure and white matter integrity many years following mild traumatic brain injury (TBI) (Kraus, Susmaras, Caughlin, Walker, Sweeney, & Little, 2007; Lo, Shifteh, Gold, Bello, & Lipton, 2009; Niogi et al., 2008; Rutgers, Toulgoat, Cazejust, Fillard, Lasjaunias, & Ducreux, 2008; Wozniak et al., 2007) and documentation of persisting memory deficits that may exist in well motivated, nonlitigating, nondepressed, ostensibly "recovered" individuals (Belanger & Vanderploeg, 2005; Gentilini et al., 1985; Iverson, Lovell, & Smith, 2000; Ponsford et al., 2000). This discrepancy has led some to question the ecological validity and sensitivity of neuropsychological assessment to detect persisting cognitive changes in patients with a history of mild TBI (Satz et al., 1999; Silver, 2000). We set out to address this disparity by comparing neuroimaging measures with verbal memory performance in a sample of nonlitigating, nondepressed, chronic, mild TBI patients. Rather than rely upon composite measures of learning and memory, we focused on trial-by-trial performance on a measure of verbal memory.

Acute mild TBI is commonly associated with symptoms including visual disturbance, sensitivity to noise/light, nausea/vomiting, and headache (Ropper & Brown, 2005) as well as alterations in cognition and behavior with specific impairments in memory (Belanger & Vanderploeg, 2005), attention (Kwok, Lee, Leung, & Poon, 2008; Rao et al., 1997), working memory (McAllister, Flashman, McDonald, & Saykin, 2006), processing speed (Willmott, Ponsford, Hocking, & Schönberger, 2009), executive functioning (Wozniak et al., 2007), and mood (Jorge, Acion, Starkstein, & Magnotta, 2007). Neuropsychological studies in acute mild TBI have demonstrated that the majority of individuals

Correspondence and reprint requests to: Deborah M. Little, Department of Neurology, MC 796, 912 South Wood Street 855 N, Chicago, Illinois 60612. E-mail: little@uic.edu

recover and that cognitive and behavioral difficulties remit over a period of weeks to months (Macciocchi, Barth, Alves, Rimel, & Jane, 1996; Maddocks & Saling, 1996; Teasdale & Engberg, 1997). While postconcussive memory complaints are frequently reported in chronic mild TBI (Sigurdardottir, Andelic, Roe, Jerstad, & Schanke, 2009), several studies in chronic mild TBI patients have included participants with psychiatric disturbance or those involved in litigation which raises questions about effort and motivation.

Memory studies in acute mild TBI have traditionally assessed memory using measures of total immediate learning and delayed recall (Chamelian & Feinstein, 2006; Ettenhofer & Abeles, 2009; Mooney, Speed, & Sheppard, 2005). These studies, having found no objective evidence of memory complaints, attributed chronic complaints to psychological or motivational factors rather than the pathophysiology of the injury itself (Ettenhofer & Abeles, 2009; Larrabee, 1997; Mooney & Speed, 2001; Mooney et al., 2005). Others have argued such methods may miss more subtle functional deficits in learning and memory experienced in chronic mild TBI (Bigler, 2008; Gioia & Isquith, 2004; Yeates & Taylor, 2005).

As a cognitive domain, memory is a highly integrated series of functions dependent on a distributed neural network. In formal neuropsychological assessments, learning and memory are characterized by juxtaposing total recall across multiple presentations with total recall following a delay. In an information-processing framework, encoding encompasses the end result of fundamental steps of both attending to and acquiring the information at first trial to the final trial. New information is deemed encoded once it is able to be recalled following both immediate presentation and following a delay (Bauer, Grande, & Valenstein, 2003). Within this specific framework, there are three crucial steps for memory formation including acquisition, encoding, and retrieval. In this model, acquisition refers to ability to recall information following a single presentation whereas encoding encompasses all information retrieved across all presentations. In the case where materials are presented only once, both acquisition and encoding reflect the same process.

Characterizing the specific nature of the memory complaint (e.g., acquisition, encoding, retrieval) is often left to a neuropsychologist. It is not uncommon to hear reports of memory deficits offered by mild TBI patients and their collaterals. Further inquiry often elicits statements such as, "he can remember if I tell him two times" coupled with the admission that under such circumstances, the patient then demonstrates an intact ability to learn and recall information. Traditional neuropsychological assessments designed to evaluate memory (i.e., mesial temporal lobe/diencephalic dependent functions) use repeated presentation of material to then make comparisons of the gross ability to encode information *versus* what information was later recalled. Given the nature of the memory complaint described by many mild TBI patients, the traditional method of neuropsychological interpretation may miss subtle, but functionally significant deficiencies in acquisition of material presented a single time. Indeed, when confronted with well-motivated, nonlitigating, nonsomatizing, nondepressed and ostensibly recovered clinical patients, the subjective day-to-day memory complaint of some with mild TBI proves perplexing.

In the current study, we explore the possibility that chronic mild TBI patients may demonstrate a subtle initial learning deficit that can be explained by changes in white matter integrity using diffusion tensor imaging (DTI). Diffuse axonal injury is the primary injury in mild TBI regardless of etiology and as such, can be used to quantify pathology providing a neuroanatomic basis for alterations in memory performance (Kraus et al., 2007). The overarching hypothesis is that patients with mild TBI exhibit decreased initial learning ability relative to healthy controls. The secondary hypothesis is that this deficit resolves with repeated presentations of material. Furthermore, in light of the speculation that cognitive complaints are at least in part attributable to psychological factors such as somatization in patients with chronic mild TBI (Chamelian & Feinstein, 2006; Suhr & Gunstad, 2002), we examined the relationship between the cognitive variables of interest, injury variables, and various mood measures.

METHODS

Participants

Forty participants with a history of mild closed head TBI (23 females, 17 males) at least 6 months from injury were recruited from the University of Illinois Medical Center *via* advertisements in the community seeking individuals who had ever sustained a closed head injury, concussion, brain injury, or traumatic brain injury. None were recruited from active clinical practice. Thirty-five healthy controls (19 females, 16 males) were also recruited from the community to match the TBI on age, years of education, years of employment, and estimated premorbid intelligence (see Table 1). Highest level of occupational achievement was determined using the Hollingshead Four Factor Index of Socioeconomic Status Occupational Scale with values ranging from 1 (e.g., menial labor) to 9 (e.g., executive) (Hollingshead, 1975). All participants provided written informed consent and experimental procedures complied with the code of ethics of the World Medical Association, the University of Illinois Institutional Review Board, and Declaration of Helsinki.

Participants (control and TBI) were excluded if they had a history of psychiatric disorder before the TBI, substance abuse/dependency, current or past litigation, failure on a formal measure of effort, or any other neurologic or medical condition that could result in cognitive changes (e.g., hypertension, severe chronic pain). Participants were not receiving any psychiatric medication or medications used for cognitive enhancement at the time of the study. The criteria used for defining mild TBI follow the guidelines set forth by the American Congress of Rehabilitation Medicine (1993)

Table 1. Participant demographics, mood and behavioral data, and frequency of reported post-concussive symptoms complaints

	Control (n = 35)		TBI (n = 40)			
	Mean	*SD*	Mean	*SD*	T value	*p* value
Demographic variables						
Age	32.54	10.77	34.53	10.22	−0.817	.416
Years of Education	16.00	1.83	16.38	2.12	−0.814	.418
Years of Employment	12.73	11.37	15.74	9.96	−1.205	.232
Hollingshead Highest Level of Employment	6.50	1.59	6.43	1.56	0.172	.864
WTAR Full Scale IQ Estimate	111.31	10.53	111.68	9.56	−0.156	.877
TOMM Trial 2	50.00	0.00	49.90	0.31	1.667	.102
Dot Counting	8.42	2.30	9.00	2.42	−0.899	.373
Employed/Student at Evaluation (% sample)	94.3%		92.5%			
Gender (M/F)	16	19	17	23		
TBI variables						
Age at TBI (years)	—	—	29.58	1.73		
Time Since Injury (years)	—	—	5.29	1.01		
Length Loss of Consciousness (N = 20) (minutes)	—	—	5.10	1.93		
Length of Post Traumatic Amnesia (N = 13) (minutes)	—	—	30.38	7.75		
Current Cognitive Complaints (% sample)	0.0%		82.5%			
Current Behavioral Complaints (% sample)	2.9%		47.5%			
Returned to Work/School Following Injury (% sample)	—		92.5%			
Mood variables						
BDI Total	3.77	5.04	11.65	10.07	−4.190	<.001
FrSBe Apathy Before (T-score)	—	—	47.58	12.92	—	—
FrSBe Apathy After (T-score)	43.74	9.83	55.98	20.37	−3.854	<.001
PCS Symptom Endorsement (often to all the time)						
Memory Problems	2.9%		47.5%			
Difficulty Concentrating	8.6%		45.5%			
Irritability	5.7%		27.5%			
Headache	0.0%		30.0%			
Fatigue	14.3%		30.0%			
Anxiety	5.7%		22.5%			
Aggravated by Noise	8.6%		20.0%			
Judgment Problems	2.9%		10.0%			
Dizziness	0.0%		12.5%			
Visual Disturbance	0.0%		10.0%			

including endorsement of at least one of the following: any period of loss of consciousness; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident (e.g., feeling dazed, disoriented, or confused); and focal neurological deficit (American Congress of Rehabilitation Medicine, 1993; Cassidy et al., 2004). For this study, participants were categorized as moderate and subsequently excluded if the duration of loss of consciousness (LOC) was greater than 30 min, post-traumatic amnesia (PTA) was greater than 24 h, there was positive radiologic finding of contusion or bleed, or evidence of skull fracture suggesting significant trauma to the head. Beyond self-report, witness reports, discharge notes from the emergency department, and previous medical records were used to confirm severity. These criteria help ensure that the only patients remaining were, in fact, mild severity (LOC less than 30 min; PTA less than 24 h, and/or the Glasgow Coma Scale greater than 13) (American Congress on Rehabilitation Medicine, 1993; Cassidy et al., 2004; Levin, 1992; Tagliaferri, Compagnone, Korsic, Servadei, Kraus, 2006). For the individuals who had information on duration of loss of consciousness and/or posttraumatic amnesia confirmed by witness reports, the average reported LOC was 5.1 min (n = 20; range, 0–30 min) and average reported PTA was 27.9 min (n = 13; range, 0–60 min). For patients without specific information regarding LOC (n = 20) or PTA (n = 27), we relied upon estimates of self-reported and witness reported of duration of LOC or PTA and discharge note diagnosis from emergency departments when available for the purpose of study inclusion only.

The mechanism of injury varied and included motor vehicle accidents (n = 10), pedestrian MVA (n = 3), assault (n = 3), sports related (n = 11), and falls or blows to the head (n = 13). No TBI patient evidenced any frank structural lesion suggestive of focal injury on neuroimaging. Fourteen patients reported experiencing more than one TBI (range, 2–7). Analyses were conducted without these 14 participants with no effect on statistical significance on learning and memory or DTI analyses. As such, all participants were included in subsequent analyses. Demographic data and injury related variables are presented in Table 1.

MATERIALS AND PROCEDURE

Neuropsychological Assessment

As detailed in prior work, participants completed an extensive neuropsychological test battery that was assembled to assess executive function, attention, and memory (Kraus et al., 2007). The California Verbal Learning Test-Second Edition (CVLT-II) was used to assess memory. Our motivation for using this tool, rather than a customized learning task, is that the CVLT-II is a widely available clinical tool. The CVLT-II consists of two different lists of words (List A and List B). Each list is comprised of sixteen words from four related categories presented in a pseudo-random manner. List A is administered five times followed immediately by the sole presentation of List B. Participants receive a point for each accurately recalled item.

Participants were also administered the Beck Depression Inventory-Second Edition (BDI-II) to assess for mood disturbance. While our TBI participants endorsed a significantly higher number of depressive symptoms than controls (see Table 1), the TBI group mean of 11.08 (SD = 10.07) is within the "minimal" depression criterion category. Concentration difficulties, sleep disturbance, and fatigue are commonly reported following mild TBI (Lundin, de Boussard, Edman, & Borg, 2006; Orff, Ayalon, & Drummond, 2009) and examination of specific BDI items found a high frequency of these items endorsed in the mild TBI group *versus* endorsement of sadness or loss of pleasure. Further review, however, also determined the presence of seven individuals in the TBI group with BDI-II scores within the moderate range (above 20). Analyses of memory and DTI variables were conducted with and without these seven participants and demonstrated no effect on the pattern of results. As such, all participants were included in reported analyses.

The Post-Concussion Syndrome Checklist (PCSC) (Gouvier, Cubic, Jones, Phillip, & Cutlip, 1992) was used to rate subjective frequency of various post-concussive symptoms (PCS). Almost half (47.5%) of the TBI participants reported experiencing memory difficulties and 45.0% reported attention/concentration problems with high frequency. During clinical interview, participants were also asked if they experienced cognitive (e.g., memory, attention) or behavioral (e.g, irritability, fatigue) difficulties. The Frontal Systems Behavior Rating Scale-Self Version (FrSBe), a self-report behavior rating scale, was used to assess for the presence of postinjury behavioral syndromes of apathy, disinhibition and executive dysfunction (Reid-Arndt, Nehl, & Hinkebein, 2007). The TBI and control participants differed only on reported current level of apathy (Table 1) with TBI participants endorsing higher rates of apathy. Finally, TBI and control participants also completed two measures of effort (i.e., Test of Memory Malingering, Dot Counting) and all participants achieved scores in the valid range on the respective measure (Table 1).

DTI Data Acquisition

Imaging studies were conducted using a 3.0-Tesla whole body scanner (General Electric Medical Systems, Waukesha, WI) using a customized DTI pulse sequence with a quadrature head coil. The DTI sequence is based on a single-shot EPI with the capability of compensating eddy currents induced by the diffusion gradients *via* dynamically modifying the imaging gradient waveforms (Poonawalla & Zhou, 2004). The sequence used 27 diffusion gradient directions, b-values of 0, 750 s/mm^2, and voxel sizes of $1.5 \times 1.5 \times 5$ mm^3. A 3D high resolution anatomical scan was also acquired to allow coregistration with the DTI data and normalization to the Montreal Neurological Institute template (MNI) with a spatial resolution of $0.85 \times 0.64 \times 1.5$ mm^3 (Kraus et al., 2007, for additional details).

DTI Data Analysis

The 28 diffusion directions were used to calculate the fractional anisotropy (FA) as the primary indicator of white matter integrity. The images were reconstructed and FA calculated using DTI Studio (Wakana et al., 2004). The 28 diffusion weighted images were examined for image quality and head movement. Head movement was required to be less than 2 mm. Voxels with very low signal (indicating nonbrain voxels) were masked out of the analysis before calculation of pixelwise FA (background noise = 125). The FA map was then converted to ANALYZE. Statistical Parametric Mapping (SPM2, Wellcome Department of Imaging Neuroscience, London, UK) Was used to co-register the DTI with corresponding T1 images and then convert the DTI to normalized space (Montreal Neurologic Institute T1 template). None of the mild TBI in this investigation had significant atrophy or pathology making normalization to the MNI template accurate.

Region of Interest Analysis

All region of interest (ROI) analyses were carried out on data from each individual participant. The ROIs were drawn on a group averaged (including both controls and mild TBI) normalized FA map referencing not only the grayscale FA map but also a color-coded directionality map. This color-coded map allows visualization of intersecting fiber bundles and provides information as to where specific tracts begin and end. The masks were then overlaid on the FA maps from the

remaining participants and visually checked for accuracy. The specific ROIs included the following: anterior and posterior corona radiata, corticospinal tracts (including parts of the corticopontine tract and superior thalamic radiation), external capsule, cingulum, forceps minor, forceps major, inferior fronto-occipital fasciculus, superior longitudinal fasciculus, uncinate fasciculus, sagittal stratum, and body, genu, and splenium of the corpus callosum. Right and left were analyzed separately where appropriate and combined when no differences reached significance. Detailed descriptions of these regions of interest can be found in (Kraus et al., 2007).

These masks were then applied to the FA map from each individual participant. One concern when using ROI masks drawn on representative participants is that either gray matter or cerebral spinal fluid would be included in the calculation of mean FA. To ensure that FA was only calculated from white matter tissue, a threshold of FA = 0.20 was applied before extraction of FA for each ROI.

Statistical Analysis

For the CVLT-II, we examined group comparisons of the first trial of List A and the single List B learning trial using independent sample *t* tests We then conducted a mixed-design repeated-measure analysis of variance with Trial as the within-subject factor (recall on Trials 1, 2, 3, 4, 5) and Group (control, TBI) as the between-subject factor. We also conducted a mixed-design repeated-measures analysis of variance (ANOVA) of single trial learning as the within-subject factor (recall on Trial 1 and List B) and Group as the between-subject factor. In addition to raw rates of recall across trials, data from each individual were fitted to a power function (Equation 1). The power function, which is commonly applied in the behavioral learning literature (Anderson, 1982; Logan, 1998), was applied to data from each participant to allow extraction of both the y-intercept (represented by *y* in Equation 1) and slope (represented by *b* in Equation 1):

$$y = ax^b \quad (1)$$

For the DTI data, tests of independent means were conducted between groups for the body, genu, splenium, and total corpus callosum. For the 11 remaining ROIs for which measurements could be taken for each hemisphere, we conducted repeated measures ANOVAs with the left/right ROI as the within-subject measures by Group (control *vs* TBI) as the between-subject comparison.

To determine the amount of unique variance accounted for by DTI variables in performance on single trial learning, ROIs that demonstrated group differences were entered into a stepwise regression analyses with CVLT Trial 1 as the dependent variable.

RESULTS

CVLT-II

To test the primary hypothesis that mild TBI show reductions in single trial learning (acquisition), an independent samples *t* test was used to compare TBI and control recall on Trial 1 of List A. The mild TBI group achieved lowers scores than the control group on the first trial of the CVLT-II (Figure 1A), $t(73) = 2.341$; $p = .020$; $\eta^2 = 0.070$.

Although there was a trend for reduced performance in TBI, a repeated-measures ANOVA demonstrated that the groups did not differ in performance across the five total immediate learning trials, $F(1,73) = 3.288$; $p = .074$; $\eta^2 = 0.043$. Additionally, there was no Group × Trial interaction. Unlike List A Trial 1, the groups did not differ on List B, $t(73) = 1.009$; $p = .317$; $\eta^2 = 0.014$ (Table 2) and repeated-measures revealed no Group × List interaction.

Further analyses of each CVLT-II trial demonstrated that the mild TBI participants were significantly different from controls on the first trial, but not on any subsequent trial (Trials 2–5) of List A. However, the analysis of slope (or

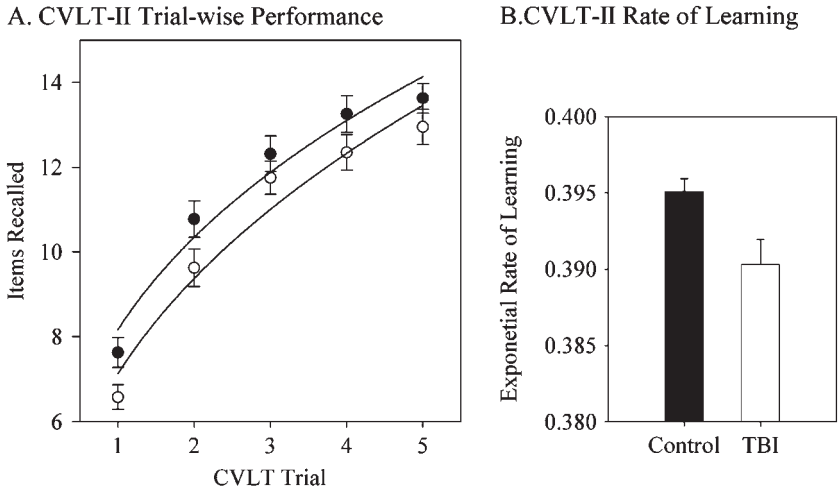

Fig. 1. California Verbal Learning Test-Second Edition (CVLT-II) learning analyses. A: CVLT-II raw recall findings across trials 1 through 5 for controls and patients with mild traumatic brain injury (TBI). Statistically significant difference between groups was only observed on the first learning trial. Lines represent best fit power function for each group. B: Average exponential rate of learning for controls and mild TBI patients. Error bars represent 1 ± SEM.

Table 2. Raw scores of California Verbal Learning Test-Second Edition (CVLT-II) performance

	Control (n = 35)		TBI (n = 40)			
	Mean	*SD*	Mean	*SD*	T value	*p* value
CVLT-II Raw Scores						
Trial 1	7.63	2.06	6.58	1.84	2.341	.022
Trial 2	10.77	2.54	9.63	2.82	1.839	.070
Trial 3	12.31	2.48	11.75	2.46	0.987	.327
Trial 4	13.26	2.57	12.35	2.65	1.501	.138
Trial 5	13.63	2.07	12.95	2.65	1.222	.226
Total Trials (T-Score)	57.60	9.84	53.25	10.80	1.813	.074
Trial B	7.11	2.82	6.50	2.46	1.009	.317
Short Delay Free Recall	12.17	3.32	11.48	2.95	0.961	.339
Short Delay Cued Recall	12.43	2.73	11.98	2.89	0.697	.488
Long Delay Free Recall	12.46	3.28	11.60	3.01	1.179	.242
Long Delay Cued Recall	13.14	2.40	12.45	2.89	1.119	.267

rate) from the individually fit power functions demonstrated a significant difference between the groups with reduced rate in the mild TBI group, $t(73) = 2.514$; $p = .014$; $\eta^2 = 0.080$ (see Figure 1B). As would be expected from the Trial 1 effect, there was also a difference in the y-intercept, $t(73) = 2.118$; $p = .038$; $\eta^2 = 0.058$ between groups. In terms of overall list learning, the groups did not differ on the total five-trial verbal learning composite score, $t(73) = 1.813$; $p = .074$; $\eta^2 = 0.043$, short-delay free recall, $t(73) = 0.961$; $p = .343$; $\eta^2 = 0.013$, or long delay free recall, $t(73) = 1.179$; $p = .242$; $\eta^2 = 0.019$. The groups performed similarly on both the cued short-delay $t(73) = 0.697$; $p = .488$; $\eta^2 = 0.007$ and long-delay, $t(73) = 1.119$; $p = .267$; $\eta^2 = 0.017$.

Analyses were also conducted comparing CVLT-II performance between TBI participants who reported memory complaints on the PCSC *versus* those who did not. As detailed in Figure 2, the TBI participants with reported memory complaints achieved lower scores on all trials of the CVLT-II than TBI without complaints (all comparisons, $p < .05$). TBI patients with subjective memory complaints also achieved lower scores on List B and the delayed memory score ($p < .05$).

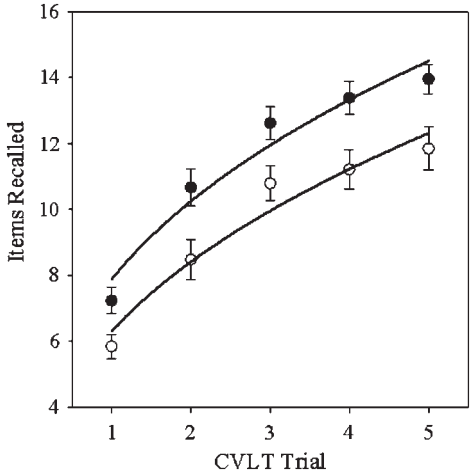

Fig. 2. California Verbal Learning Test-Second Edition (CVLT-II) learning by traumatic brain injury (TBI) with and without memory complaints. CVLT-II raw recall findings across trials 1 through 5 for TBI patients with (filled circles) and without (open circles) memory complaints as measured by the PCSC.

Relationship between Verbal Learning and Mood

Pearson product-moment correlations found no relationship between initial verbal learning with total BDI-2 depression score ($r = -0.059$; $p = .715$), frequency of PCS anxiety ($r = -0.046$; $p = .907$) and FrSBe ratings of apathy after injury ($r = -0.133$; $p = .420$). There was also no relationship detected between the composite total learning score or any delayed memory variables with depression, anxiety, or apathy (all p's > .05).

Neuroimaging-DTI Analysis

Consistent with earlier findings (Kraus et al., 2007) and as depicted in Figure 3A–C, the mild TBI group had significantly lower FA compared with controls in the superior longitudinal fasciculus, $F(1,73) = 4.608$; $p = .035$; $\eta^2 = 0.059$, sagittal stratum, $F(1,73) = 5.695$; $p = .020$; $\eta^2 = 0.072$, and uncinate fasciculus, $F(1,73) = 10.600$; $p = .002$; $\eta^2 = 0.127$. The TBI group did not differ from controls in any other ROI.

Relationship Between DTI and Single Trial Learning

Linear regression analyses were conducted to determine the amount of unique variance that FA in these ROIs could account for in the single-trial learning measure. These analyses demonstrated that only FA of the left uncinate fasciculus, $t(39) = 2.549$; $p = .016$ and left superior longitudinal fasciculus $t(39) = 2.059$; $p = .047$ accounted for a significant amount of variance (14% and 9%) in the first learning trial of the CVLT-II. However, neither ROI was a significant predictor of total learning, learning rate, or short or long

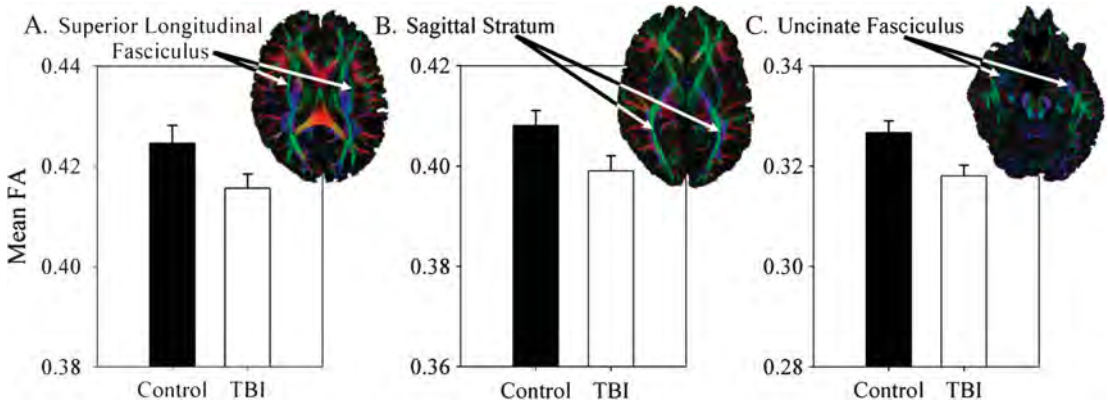

Fig. 3. Fractional anisotropy (FA) by group comparisons. Mean FA for the left/right superior longitudinal fasciculus (A), left/right sagittal stratum (B), and left/right uncinate fasciculus (C) for controls and mild TBI participants.

delay memory performance (all *p*'s > .05). Table 3 details the Pearson-product moment correlations between the remaining ROIs, single-trial learning measures, sustained attention measures, and mood and behavior variables.

DISCUSSION

The individual components of memory (i.e., attend, acquire, encode, consolidate, and recall information) are likely not given much consideration by an individual who reports "memory" problems; an individual simply experiences a failure to remember. If an individual is unable to initially acquire information following one trial, the memory complaint is of the same verisimilitude as that experienced by an individual with an impaired ability to encode information over many trials. In daily interactions such as conversations, lectures, and work-place instructions, individuals are often presented with information one time, rather than being given the benefit of repeated "trials." For this reason and others, studies have questioned the ecological validity of composite learning and memory domain scores in elucidating the nature of memory complaints following TBI (Silver, 2000; Silverberg & Millis, 2009; Wood, 2009; Yeates & Taylor, 2005)

Consistent with our hypothesis, participants with a history of chronic mild TBI did differ significantly from the control participants on a measure of initial verbal learning (acquisition). Furthermore, there was no significant group difference on the total composite learning score or delayed memory variables. Taken together, despite reported memory difficulties by 47% of the mild TBI participants, these findings suggest no generalized deficit in the broadly conceptualized memory system per se. The TBI participants were able to encode information over the five trials; what they did encode, they were able to recall. Given the objective finding of differences on Trial 1 and slower rate of overall learning, interpreting only the total immediate or delayed memory scores on the CVLT-II may not be ecologically valid. The mild TBI patients demonstrate an inefficiency when presented with information for the first time which could easily be exacerbated by the qualities of day-to-day interaction *versus* constitute a generalized encoding, consolidation, and/

Table 3. Significant bivariate correlation in regions of interest with cognitive and behavioral variables

	ACR		PCR		fMin	fMaj	EC	UF		CG	SS	CST	
Hemisphere	L	R	L	R	L	R	R	L	R	R	L	R	gCC
CVLT													
Trial 1					.452**			.336*		.316*			
Trial 2	.376*	.346*			.419**	.327*							
Trial 3	.321*												
Trial 4	.319*				.321*								
Trial 5													
List B	.324*	.353*			.446**								.386*
BDI Raw Score												.323*	
FrSBe Apathy							.419**	.	325*				
PCSC Total			.416*	.505**			−.355*				.373*		

**p = 0.01 level
*p = 0.05 level
Note. ACR = anterior corona radiata; PCR = posterior corona radiata; fMin = forceps minor; fMaj = forceps major; EC = external capsule; UF = uncinate fasciculus; CG = cingulum; SS = the sagittal stratum including the optic radiations; CST = corticospinal tracts, which included parts of the corticopontine tract and parts of the superior thalamic radiation; gCC = genu corpus callosum.

or retrieval-based "memory" deficit. These findings have translational value in that they support clinical recommendations such as rehearsal of information to facilitate encoding and recall.

While historically considered a "benign" injury with complete recovery expected within 3 months (Carroll et al., 2004; Lange, Iverson, & Franzen, 2009; Levin et al., 1987), it is believed that a minority of individuals experience postconcussive symptoms beyond this period (Pagulayan, Temkin, Machamer, & Dikmen, 2006; Rothweiler, Temkin, & Dikmen, 1998; Sterr, Herron, Hayward, & Montaldi, 2006; Vanderploeg, Berlanger, & Curtiss, 2009; Vanderploeg, Curtiss, & Belanger, 2005; Wood, 2004). That mild TBI is the casual factor underlying these complaints is controversial, especially given the inconsistent objective evidence supporting the complaints (e.g., evidence of neuropsychological impairment, observable lesions on MRI). Furthermore, in part because postconcussive symptoms are not specific to traumatic brain injury (Lees-Haley, Fox, & Courtney, 2001; Smith-Seemiller, Fow, Kant, & Franzen, 2003), some clinicians have suggested that the majority of complaints are complicated by or solely attributable to psychological or motivational factors rather than involve, at least in part, the pathophysiology of the injury itself (Bay & Bergman, 2006; Ettenhofer & Abeles, 2009; Jacobson, 1995; Karzmark, Hall, & Englander, 1995; Larrabee, 1997; Mooney & Speed, 2001; Mooney et al., 2005; Williams, Lees-Haley, & Brown, 1993). In fact, many studies demonstrate that psychiatric comorbidities influence PCS reporting and reports of memory complaints (Chamelian & Feinstein, 2006; Suhr & Gunstad, 2002; Vanderploeg et al., 2009). However, our data suggests Trial 1 differences exist independently of primary mood disturbance, apathy, or anxiety. Moreover, CVLT-II Trial 1 did not correlate significantly with any TBI grading parameters (e.g., duration of posttraumatic amnesia, duration of loss of consciousness, posttraumatic seizures, posttraumatic headache) as it has in other studies (MacKenzie et al., 2002). It is important to note that this lack of relationship may reflect the accuracy of self-report rather than a lack of true relationship. Most critically, the finding of diminished recall for Trial 1 was observed in well motivated (i.e., as assessed by effort measures), nonlitigating, nondepressed, and gainfully employed individuals many years after sustaining a mild TBI.

Of interest is the lack of significant difference between groups on the second word list (List B). Initially, we speculated that increased task familiarity would explain improved performance for both groups. However, this was not the case. In fact, as detailed in Table 2, the TBI participants performed at a comparable level on both Trial 1 of List A and List B where control participants declined slightly. One alternative explanation for the lack of improvement on List B may be attributed to proactive interference (PI) effects which are common in semantic clusters (Delis, Kramer, Kaplan, & Obers, 2000). Based on the performance of the normative sample of the CVLT-II and other patient populations (Ivory, Knight, Longmore, & Caradoc-Davie, 1999), PI effects are expected and demonstrated when the number of words recalled on the single trial of List B is lower than what was recalled on the first trial of List A (Delis et al., 2000). In our sample, the lack of a significant difference between groups on List B may illustrate the expected modest PI effects demonstrated by the control participants and the lack of PI effects in the TBI participants. While the repeated measures analysis did not demonstrate a significant group by trial interaction effect, this may have been due to lack of power, but raises a question of whether there is a reduction in PI in mild TBI.

The question is then raised as to the underlying mechanism for slower acquisition on Trial 1. In mild TBI, acceleration–deceleration forces and related diffuse axonal injury is generally found to be the only significant pathology (Bazarian, Zhong, Blyth, Zhu, Kavcic, & Peterson, 2007; Inglese et al., 2005; Medina et al., 2006). Given the nature of diffuse axonal injury and its potential impact on distributed neurobehavioral networks, injury along these pathways could result in wide-spread cognitive and behavioral dysfunction. In examining ROIs which demonstrated differences in FA relative to controls, the left uncinate fasciculus accounted for a significant amount of variance in Trial 1. This specific tract has been implicated previously in studies of memory (Niogi et al., 2008). The uncinate fasciculus connects temporal and prefrontal areas so it is not surprising to find its involvement in learning and memory. The relationship between memory and FA of the uncinate fasciculus has been demonstrated in patients with TBI (Niogi et al., 2008) with poor memory performance being correlated with reduced FA. While our data did not demonstrate a significant difference between groups on overall memory performance or a relationship between memory performance and the uncinate fasciculus, our data did demonstrate a significant relationship between Trial 1 and the left uncinate fasciculus.

Similarly, the relationship between Trial 1 performance and FA in the superior longitudinal fasciculus is also to be expected as this tract is thought to be composed of three component parts and has been purported to play a role in visual awareness, maintenance of attention, initiation of complex motor behavior, phonemic and articulatory aspects of language, and lexical decision making (Gold, Powell, Xuan, Jiang, & Hardey, 2007; Schmahmann, Smith, Eichler, & Filley, 2008). Damage to this tract has also been reported previously in TBI (Bendlin et al., 2008; Cho et al., 2008; Kraus et al., 2007). In our study, FA of the left superior longitudinal fasciculus was a significant predictor of Trial 1 performance. To our knowledge, this is the first study to demonstrate the involvement of this tract in verbal learning in TBI. Integrity of this tract has also been reported to have a role in other verbally mediated tasks such as verbal repetition (Breier, Hasan, Zhang, Men, & Papanicolaou, 2008), which may explain its involvement in the CVLT-II.

The slower rate of learning across trials in TBI warrants further investigation. Again, we would suspect that successful recall of items is influenced by how well one consistently uses a recall strategy (Chan, Kwoka, Chiub, Lamb, Pangb, & Chow, 2000; Gongvatana, Woods, Taylor, Vigil,

Table 4. California Verbal Learning Test-Second Edition (CVLT-II) standard scores

	TBI (n = 40)		% Participants	% Participants
	Mean	*SD*	1–2 *SD* below mean	>2 *SD* below mean
CVLT-II Z-scores				
Trial 1	−0.51	0.89	27.5%	—
Trial 2	−0.45	1.11	22.5%	7.5%
Trial 3	−0.23	0.99	12.5%	5.0%
Trial 4	−0.35	1.03	10.0%	5.0%
Trial 5	−0.33	1.28	12.5%	7.5%
Trial B	−0.22	0.87	12.5%	2.5%

Grant, & Group, 2007; Luek, 1976; Ribeiro, Guerreiro, & De Mendonça, 2007). It is possible that the TBI group was slow to recognize and then use a successful strategy, or they adopted a less efficient strategy (e.g., serial recall) across trials. Examining the strategic and arguably, higher-order (i.e., executive/frontal lobe), aspects of learning could be informative in appreciating the complexities of the initial verbal learning inefficiency (Wood, 2009). Our groups did not differ on formal neuropsychological measures of executive function. However, the administered executive tasks are partially externally facilitated (e.g., changing visual sorting contingencies, visual planning to match a model) and do not require the same internally derived strategy formation used in verbal list learning. However, without an analysis of the strategies used within trial and across trials on the CVLT-II, this contention is speculative. Future work will test the validity of this hypothesis.

Another concern in many TBI studies is the inclusion of participants with a history of mild TBI without witness confirmation of LOC or PTA. Given the reliance on retrospective report, it is possible that some of these individuals did not sustain a TBI. Indeed, *post hoc* analyses examining differences between control participants and the mild TBI subgroups (witness corroborated *vs* only subjective report of TBI) on the data presented herein found that significant differences on Trial 1 were only observed between controls and TBI patients with witness corroborated TBI. A study with restrictions to inclusion for only witnessed or objectively verified TBI parameters would be compelling. However, the inclusion of self-reported participants in this study only serve to increase the likelihood of supporting the null hypothesis rather than biasing in favor of finding group differences. Similarly, only approximately half of our mild TBI participants reported memory difficulties suggesting that the data presented may actually underestimate the magnitude of the effect. Consistent with this, when converted to standardized scores, these patients fall into the low end of normal performance (Table 4). Indeed, the 19 TBI participants, who reported experiencing memory difficulties, performed more poorly on all CVLT-II learning variables and likely represent the more severe end of the mild TBI continuum.

Finally, 14 TBI participants reported a history of multiple mild TBI. While analyses conducted without these individuals did not change the significance of the findings, their inclusion raises the possibility that findings could be driven, in part, by changes attributable to multiple mild injuries as has been suggested by others (Weber, 2007).

To our knowledge, this is the first study to examine verbal learning with a focus on single-trial learning and white matter integrity in a nonlitigating, nondepressed, employed population with mild TBI. Our data suggest that chronic mild TBI patients demonstrate deficits in the acquisition of information which are supported by evidence of chronic damage to white matter microstructure. However, we collected no data regarding the functional significance of any cognitive complaints and as such it is unclear if initial trial learning difficulties relate to functional deficits. Future studies comparing initial learning and more specific outcome variables (e.g., difficulties at work/school) would prove especially informative in this regard.

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Appendix 3

Manuscript Under Review – Do Not Cite

Verbal Learning Strategy in Chronic Mild Traumatic Brain Injury

Elizabeth K. Geary [1,6], Marilyn F. Kraus [1,2,7], Leah Rubin[2,7], Neil H. Pliskin [1,2,7], & Deborah M. Little [1,3-7]

From the Departments of [1]Neurology, [2]Psychiatry, [3]Anatomy, [4]Ophthalmology & [5]Psychology

and

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Corresponding Author:

Deborah M. Little PhD

Department of Neurology, MC 796

912 South Wood Street 855 N

Chicago, Illinois 60612

Phone: 312-355-5405

Fax: 312-355-5444

Email: deborahmlittle@gmail.com

ABSTRACT

That learning and memory deficits persist many years following mild traumatic brain injury (TBI) is controversial due to inconsistent objective evidence supporting subjective complaints. Our prior work demonstrated significant reductions in performance on the initial trial of a verbal learning task in well-motivated mild TBI participants relative to demographically matched controls. In our original work, we speculated that differences in strategy use could explain the initial verbal learning discrepancies. The current study serves to test this hypothesis by examining strategy use on the California Verbal Learning Test-Second Edition. Our present findings support the primary hypothesis that mild TBI participants under-utilize semantic clustering strategies relative to control participants. Although there were no differences in strategy use for the initial two trials, mild TBI participants showed reductions in semantic clusters on the third and subsequent trials. We posit that the chronic learning and memory difficulties reported by some mild TBI patients are related to this reduced utilization of internally-driven strategies that facilitate learning and enhance recall. Given that strategy training has demonstrated improvements in learning and memory in educational and occupational settings, we offer that these findings have translational value in offering an additional approach to remediation.

INTRODUCTION

That learning and memory difficulties are an acute consequence of mild traumatic brain injury (TBI) is well supported. That these deficits persist years following injury, however, is a controversial issue. While the majority of individuals do not appear to experience persisting cognitive difficulties after mild TBI, a subset of mild TBI patients do demonstrate such difficulties (Benedictus, Spikman, & van der Naalt, 2010; Ponsford et al., 2000) . For a myriad of complex reasons (e.g., psychological, motivational), this subset proves a challenge for clinicians. Prior work conducted in our laboratory using a non-clinical, non-litigating, chronic sample of mild TBI patients attempted to address issues related to memory complaints often raised by clinical patients and their families (Geary, Kraus, Pliskin, & Little, 2010). Our previous work focused on trial-by-trial performance on a measure of verbal learning and memory in a sample of community-recruited mild TBI participants. We reported that mild TBI patients demonstrated diminished acquisition on the initial learning trial and evidenced an overall slower rate of learning across trials in the context of equivalent performance relative to controls on the total learning and memory indices (Geary et al., 2010). Further, performance on this verbal learning task was related to imaging measures showing a relationship between the effects of injury on cerebral white matter integrity and behavioral performance. One limitation of our previous work was that we were unable to comment on the specific mechanism that may underlie this finding; we proposed the hypothesis that higher-order strategy use might underlie the initial verbal learning deficiency.

Examining higher-order "metacognitive" strategies has particular relevance in patient populations including mild TBI where evidence of chronic primary temporal lobe/diencephalic memory dysfunction is not generally supported using standardized methods (Dikmen et al., 2009; Ettenhofer & Abeles, 2009; Iverson, 2005; Schretlen & Shapiro, 2003; West, Curtis, Greve, & Bianchini, 2010) . However, others have argued that memory deficiencies in TBI could be influenced by higher-order frontal-subcortical dysfunction (Alexander, Stuss, & Gillingham, 2009; Bruce & Echemendia, 2003; Little et al., 2010). Specifically, in the realm of learning and memory, higher-order functions such as restructuring

information via the identification of shared relationships between items and/or other internally-driven mnemonic devices increase one's ability to learn and recall information (Becker & Lim, 2003; Schefft, Dulay, & Fargo, 2008). Studies in TBI and other neurologic populations have provided evidence that successful recall of items on list-learning tasks is influenced by how well one consistently employs an efficient (i.e., semantic, subjective) recall strategy (Bruce & Echemendia, 2003; Chan et al., 2000; Gongvatana et al., 2007; Gsottschneider et al., 2010; Luek, 1976; Ribeiro, Guerreiro, & De Mendonça, 2007).

When conceptualizing metacognitive strategies hierarchically in terms of degree of cognitive engagement, semantic clustering arguably constitutes the most sophisticated strategy. Semantic clustering encompasses mentally grouping items from the same taxonomic category at greater than chance levels and is most often associated with improved learning and recall (Delis, Freeland, Kramer, & Kaplan, 1988). In order for semantic clustering strategies to be employed, an individual must first identify that semantic relationships exist, employ the strategy by compartmentalizing words during list encoding, and then utilize the semantic groups during both initial and subsequent recall. In list-learning tasks such as the California Verbal Learning Test (CVLT-II), this process involves recognizing that the pseudo-random presentation of sixteen target words consists of items from four semantic categories, regrouping words according to these four categories, and organizing words within these clusters during later learning and recall trials.

In contrast to semantic clustering, subjective clustering may involve restructuring the list based on phonemic features of items or another personally derived mnemonic. Because of this internally derived strategy, identification of subjective clustering is identified when one recalls two or more words together from one trial to the next independent of standard semantic or serial clustering strategies.

Finally, serial clustering, or recalling words in the order of presentation, may partially reflect the tendency to recall the first words and last words presented (primacy/recency effects). Of all three strategies, serial clustering requires the least amount of cognitive engagement as the structure is externally derived and no mental reorganization of the list is required. If used at the exclusion of the other two

strategies, serial clustering tends to be the least efficient as it often results in poorer performance (Delis et al., 1988). Serial clustering is often most readily applied across trials in memory impaired populations (Gsottschneider et al., 2010; Jefferies, Hoffman, Jones, & Ralph, 2008; Ranjith, Mathuranath, Sharma, & Alexander, 2010).

In our prior work, we speculated that differences in rate of learning between groups could result if the TBI group was slow to recognize and then employ an efficient learning strategy across trials (Geary et al., 2010). The purpose of the present investigation is to test the hypothesis that mild TBI participants utilize semantic clustering less often than controls using the California Verbal Learning Test-Second Edition (CVLT-II). Conversely, in our secondary hypothesis, we offer that the slower learning rate across trials between mild TBI participants and controls would be explained by use of the less efficient serial clustering strategy.

METHODS

Participants

From a larger sample of participants described previously (Geary et al, 2010), CVLT-II response data was available and analyzed for a total of 35 TBI participants (19 females) and twenty-eight healthy controls (15 females). All participants provided written informed consent and experimental procedures complied with the code of ethics of the World Medical Association, Declaration of Helsinki, and Institutional Review Board. Participants were excluded if they had a history of psychiatric disorder before the TBI, substance abuse/dependency, current or past litigation, failure on a formal measure of effort, or any other neurologic or medical condition that could result in cognitive changes (e.g., hypertension, severe chronic pain). No participants were recruited from active clinical practices for treatment of TBI. Participants were not receiving any psychiatric medication or medications used for cognitive enhancement at the time of the study. The criteria used for defining mild TBI follow the guidelines set forth by the American Congress of Rehabilitation Medicine (ACRM, 1993) including endorsement of at least one of the following: any period of loss of consciousness; any loss of memory for events immediately before or after the accident; any alteration in mental state at the time of the accident

(e.g., feeling dazed, disoriented, or confused); and focal neurological deficit (Cassidy et al., 2004; ACRM, 1993). Beyond self-report, witness reports, discharge notes from the emergency department, and previous medical records were used to confirm severity when available. These criteria help ensure that the only patients remaining were, in fact, mild severity (LOC less than 30 minutes; PTA less than 24 hours, and/or the Glasgow Coma Scale greater than or equal to 13) (ACRM, 1993; Cassidy et al., 2004; Levin, 1992; Tagliaferri, Compagnone, Korsic, Servadei, & Kraus, 2006). For the individuals who had information on duration of loss of consciousness and/or post-traumatic amnesia confirmed by witness reports, the average reported LOC was 5.7 minutes (N=17; Range=0-30minutes) and average reported PTA was 33.5 minutes (N=10; Range=0-60minutes). For patients without specific information regarding LOC (N=18) or PTA (N=25), we relied upon estimates of self-reported and witness reported of duration of LOC or PTA and discharge note diagnosis from emergency departments when available for the purpose of study inclusion only. It is also important to note that these criteria reduce the risk of Type I error as the inclusion of no minimum LOC raises the possibility that participants classified as TBI may not have sustained a brain injury. We adopted this more conservative approach to ensure that we did not bias data in favor of the study hypothesis by including those who may have had more severe injuries.

The mechanism of injury for the TBI participants included motor vehicle accidents (MVA; N=9), pedestrian versus MVA (N=2), assault (N=3), sports-related (N=10), and falls or blows to the head (N=11). No TBI patient evidenced any frank structural lesion suggestive of focal injury on neuroimaging based upon review of both T2- and T1-weighted magnetic resonance imaging. Twelve patients reported experiencing more than one TBI (range 2-7). Analyses were conducted without these participants with no effect on statistical significance on trial 1 learning or memory analyses. Comparison between the multiple mild and single mild TBI participants did not reveal any significant differences between the groups on any semantic, serial, subjective clustering variable of interest (all p's >0.05). Given that the purpose of this study was to elaborate on findings from the originally published work, and the original findings were supported regardless of the inclusion of multiple TBI patients, we did not exclude on the

basis of history of multiple mild TBI. As such, all participants were included in subsequent analyses. Demographic data and injury related variables are presented in Table 1.

[INSERT TABLE 1 HERE]

Materials and procedure

Neuropsychological Assessment

As detailed in prior work, participants completed an extensive neuropsychological test battery that was assembled to assess executive function, attention, and memory (Kraus et al., 2007). The California Verbal Learning Test-Second Edition (CVLT-II) was used to assess list-learning and memory. The CVLT-II consists of two different lists of words (ListA and ListB). Each list is comprised of sixteen words from four related categories presented in a pseudo-random manner. ListA is administered five times followed immediately by the sole presentation of ListB. Participants receive a point for each accurately recalled item. In addition to capturing the amount of verbal information an individual can learn and recall, the CVLT-II measures many qualitative elements of precisely how information is learned (Delis, Kramer, Kaplan, & Obers, 2000). We examined these various qualitative CVLT-II recall strategies across learning trials.

Calculation of Clustering Scores

Semantic Category Clustering Individual Trials:

Semantic clustering involves recalling two or more words by virtue of shared semantic category. Recent theories of semantic clustering argue that organization processes occur during list-learning, presumably as semantic categories are identified. Semantic cluster scores were calculated based on the list-based measure of observed minus expected clustering offered by Stricker et al (2002) which was recently demonstrated to show improved classification rates when used with clinical samples (Delis et al., 2010). For scoring observed semantic clusters, one point is given for each correct semantic cluster (i.e., each pair of words from the same semantic category), for a maximum of 12 points for each trial (i.e., three points possible for each of four semantic categories). For example, successive recall of the words *cat/dog/fish* would yield an observed semantic cluster score of two. The chance-adjusted semantic

clustering score used in analyses is the observed semantic clustering score minus the expected semantic clustering score. To calculate expected semantic clustering score, we adopted the method illustrated in Equation 1 (Delis, Kramer, Kaplan, & Obers, 2000).

Eq. 1. $$\text{Expected Sem Cl}i = \frac{[(r-1)(m-1)])}{N_L-1}$$

where, "i" represents a given trial, "r" the number of correct words recalled on trial i, "m" represents the number of members of each semantic category on the original list, and "N_L" the total number of words on the original list. As such, the chance adjusted scores can range from a high of 9.0 (prefect semantic clustering with a total recall score of 16) to a low of -3.0 (no observed semantic clustering with a total recall score of 16) (Delis et al., 2000).

Subjective Clustering Individual Trials:

Subjective clustering involves word pairs recalled together from one trial to the next, which do not adhere to semantic or serial clustering strategies. For example, subjective clusters may consist of seemingly unrelated words, which have been grouped using some mnemonic by the individual (e.g., *car* full of *lettuce*) or words that share phonemic qualities (e.g., *chair/cat*; *sofa/soup*). The observed bidirectional subjective clustering score includes any target words recalled together (either in forward order or backward order) across two consecutive trials. The expected subjective clustering score is calculated using the method illustrated in Equation 2.

Eq. 2. $$\text{Expected Subj Cl}ii = \frac{[(2c)(c-1)]}{hk}$$

The expected value consists of "ii" which represents the subjective clustering score between two given trials, "c," which is the number of common items recalled in Trials t and t + 1 (regardless if grouped together), "h," which is the number of recalled items in Trial t, and "k," which is the number of items recalled in Trial t +1 (Sternberg & Tulving, 1977). The chance-adjusted subjective clustering score used in analyses is the observed subjective clustering score minus the expected subjective clustering score. An example is if the word pair *car/lettuce* (subjective observed score of 1) is recalled together on trial one

and trial two with 8 total words correctly recalled on trial one (t=8) and 9 total words correctly recalled on the trial two (t+1=9). If there were 4 words in common across both trials (but only one subjective cluster), the subjective clustering expected score would be calculated using: c= 4 (4 words recalled on both trial 1 to trial 2), h= 8 as trial 1 had 8 total correct words recalled, k= 9 as trial 2 had 9 total correct words recalled: 2(4)* (4-1)/ (8*9)= 0.333. This result is then inserted into the chance adjusted subjective clustering formula of observed subjective clustering (*car/lettuce*, subjective observed score of 1) minus expected subjective clustering or [1-0.333]= 0.667, yielding a subjective clustering score of 0.667 for trial 1 to trial 2. A higher number demonstrates greater frequency of subjective clustering.

Serial Clustering Individual Trials

Serial clustering encompasses recalling items in the order in which they were presented. The serial position effect (Young, Hakes, & Hicks, 1965) is demonstrated by a tendency to recall more items from the first (i.e., primacy) and last (i.e., recency) portions of a word list. On the CVLT-II, a serial recall *strategy* is an extension of the serial position effect as it involves grouping items in the order in which they were presented. For serial cluster scoring, one point was given each time two correct items from the list are recalled in the same order in which they were presented (serial forward). For example, successive recall of the first, second and third words would yield a serial forward order score of two. We also scored serial clusters backward for one point every time a correct target word immediately follows another correct target word in reverse order. For example, a recall of the sixteenth and fifteenth words would yield at backward serial score of one.

The bidirectional serial clustering observed score encompasses a summation of observed forward (F) serial clustering and observed backward (B) serial clustering. The chance adjusted serial clustering score is illustrated in Equation 3:

Eq. 3. $$(\text{Observed F+B Serial Cl}i) - \text{Expected Serial Cl}i = \frac{[(c-1)]}{16}$$

where "i" is represents a given trial and "c" is the number of correctly recalled items for the trial. The chance adjusted serial score thereby reflects bidirectional serial clustering observed minus bidirectional serial clustering expected.

Statistical Analysis

For the strategic learning measures, we conducted three separate mixed factor analyses of variance (i.e., one per clustering strategy). We used the strategy score for each trial as the within-subject factor (e.g., semantic/serial clustering score on five trials: 1, 2, 3, 4, 5; subjective clustering scores only in 4 trials: trial 1 to trial 2; trial 2 to trial 3; trial 3 to trial 4; trial 4 to trial 5) and Group (control, TBI) as the between-subject factor. Also, as described previously (Geary et al., 2010), data from each individual were fitted to a power function (Equation 4). The power function, which is commonly applied in the behavioral learning literature (Anderson, 1982; Logan, 1998), was applied to data from each participant to allow extraction of both the y-intercept (represented by *y* in Eq. 4) and slope (represented by *b* in Eq. 4).

Eq. 4. $y=ax^b$

These values were then entered into a step-wise regression analysis to determine which, if any, of the three clustering strategies averaged over the five trials could explain overall rate of learning.

RESULTS

Consistent with our prior reported observations, the groups did not differ in raw score performance across the five total learning trials, $F(1,61)=3.255$, $p=0.076$, $\eta^2=0.051$, and there was no significant group by trial interaction ($p= 0.443$). However, groups did differ on performance on the initial learning trial of the CVLT-II ($t(61)= 2.576$, p= 0.012). This relationship is shown in Figure 1A. Groups did not differ significantly on total learning or delayed memory scores or ListB recall (all p's >0.05).

[INSERT FIGURE 1 HERE]

To test our primary hypothesis that the differences in trial by trial learning are due to differences in the degree the groups utilize semantic clustering, we conducted a mixed factor ANOVA of chance adjusted semantic clusters scores across the five learning trials between groups. This analysis

demonstrated a significant between group effect with control participants utilizing more semantic clusters compared to mild TBI participants $F(1,61)=4.872$, $p= 0.031$, $\eta^{2=}$ 0.075. As shown in Figure 1B, there was no significant group by trial interaction effect ($p= 0.127$). Post-hoc independent *t*-tests using the mixed effects error term revealed no significant between groups differences on learning trials 1-2, but significant differences on trials 3-5 with the control participants utilizing more semantic clusters relative to mild TBI. We did not include ListB in our primary analyses as it is difficult to reliably analyze strategy use in only one presentation. However, to examine potential transfer of strategy (DeRosa et al., 1970), we conducted a post-hoc mixed factor analysis comparing ListA Trial 1 semantic clustering to ListB semantic clusters which revealed no significant interaction, but did show a significant between group effect with controls utilizing more semantic clusters $F(1,61)=8.059$, $p=0.006$, $\eta^2=0.118$. Postdoc independent t-tests revealed significant between group difference on ListB semantic clustering with controls using more semantic clusters relative to mild TBI participants $t(61)= 2.760$, $p= 0.008$, $\eta^2= 0.113$.

To examine subjective clustering across trials, a mixed factor ANOVA was conducted examining trials 1-2, trials 2-3, trials 3-4, and trials 4-5 (adjusted for total words consistently recalled on both trials). As is illustrated in Figure 1C, this analysis demonstrated no significant group by trial interaction and no significant between group difference on subjective clustering $F(1,61)= 0.060$, $p= 0.807$, $\eta^{2=}$ 0.001.

Serial clustering was also examined and is presented in Figure 1D. A mixed factor ANOVA was utilized examining chance adjusted bidirectional serial clustering across learning trials. This analysis revealed no significant group by trial interaction difference of serial clustering across trials or between the mild TBI and control participants $F(1,61)= 0.157$, $p= 0.693$, $\eta^{2=}$ 0.003.

Our secondary hypothesis was that clustering strategy could explain performance on CVLT-II learning rate. A stepwise linear regression analysis was undertaken entering the average five trial semantic clustering score, average five trial bidirectional serial clustering score, and average of four subjective clustering scores, as predictors of rate of overall learning. These analyses revealed that for the mild TBI participants, only the average serial clustering score was a significant predictor of learning rate ($t(34)= 2.594$, $p= 0.014$) accounting for 18% of the variance in learning rate. Neither the average

semantic clustering score nor the average subjective clustering score predicted rate of learning (all p's>0.05). As detailed in Table 2, examining the zero-order correlations for total learning across trials for mild TBI participants found that subjective (r=0.556, p=0.000) and serial (r=0.476, p=0.002) clustering scores were highly correlated with total overall learning rate; semantic clustering score did not correlate with total overall learning rate (p= 0.105). For control participants, however, average semantic (r=0.571, p=0.001) and average subjective (r=0.560, p=0.001) clustering scores were highly correlated with total overall learning rate; serial cluster score was not correlated with total overall learning rate (p= 0.379).

[INSERT TABLE 2 HERE]

DISCUSSION

The current study serves to characterize the mechanisms that underlie verbal learning in mild TBI and specifically the strategies that result in reductions in recall on the initial trial in mild TBI (Geary et al., 2010). To our knowledge, this is the first study to examine verbal learning strategy use within and across trials in a chronic mild TBI sample who achieved comparable total learning and memory scores relative to control participants. This approach is consistent with recent interest examining qualitative aspects of performance, such as strategy use (Millis & Ricker, 1994; Nolin, 2006; Schefft et al., 2008). Semantic and subjective strategy formation and implementation are considered qualitative aspects of learning and memory performance. Such behaviors fall under the rubric of executive functions (Alexander & Stuss, 2006; Matsui et al., 2008) reflective of active engagement of self-generated or internally driven reasoning skill. Semantic clustering arguably represents the most efficient and highest-order organization strategy to facilitate learning (Becker & Lim, 2003). Given the evidence of frontal lobe dysfunction and reduced strategy use in TBI of greater severity (Levine et al., 1998; Millis & Ricker, 1994; Schefft et al., 2008; Strangman et al., 2008), we questioned if a lack of internally-driven metacognitive strategy use could explain diminished initial acquisition and decreased rate of learning across trials in a chronic mild TBI sample. Our present findings are supportive of the hypothesis that mild TBI participants are under-utilizing a semantic clustering strategy relative to control participants. While there was no significant group differences on semantic clusters on the initial two learning trials, by

the third and subsequent trials, control participants utilized more semantic clusters compared to the mild TBI participants.

Metacognitive strategy also includes the awareness that strategy use facilitates learning/recall on a word-list and then utilizing that strategy in another word-list (Ellis, 1965). In the CVLT-II, transfer of learning strategy is likely evident when semantic clustering is employed both during ListA learning trials and on the single presentation of ListB (DeRosa, Doane, & Russell, 1970). Our groups did not differ on total raw recall on ListB or, as reported previously, there were no between group difference or interaction effect evident on repeated ANOVA comparing ListA trial 1 to ListB raw recall performance. However, post-hoc analyses revealed that control participants employed significantly more semantic clusters on ListB relative to TBI participants. ListB presentation immediately follows the fifth ListA learning trial and consists of sixteen items from four semantic categories, two categories overlap with categories on ListA. Despite proactive interference effects which are greatest among words from shared semantic categories (Delis et al., 2000), the results of the mixed ANOVA found that control participants use more semantic clusters on ListB relative to TBI participants. This finding offers additional support that the mild TBI participants exhibit deficient semantic strategy use as they do not generalize the semantic clustering strategy to a novel word list.

Employing a serial clustering strategy does not involve actively restructuring information as it is presented. Rather, serial clustering strategy is externally facilitated as it embodies recalling items in the order in which they are presented. An over-reliance on serial clustering, at the expense of semantic clustering, in other neurological populations has been demonstrated to negatively correlate with overall recall (Delis et al., 1988; Gsottschneider et al., 2010; Jefferies et al., 2008; Ranjith et al., 2010). Our present findings are consistent with our hypothesis that mild TBI participants employ a less efficient serial strategy relative to controls. For mild TBI participants, averaged serial clustering was the only significant predictor of learning rate over trials.

That mild TBI participants employ less semantic clusters relative to controls and utilize more serial strategies is compelling especially given the lack of significant group differences on total raw recall

on learning trials 2-5 and comparable total learning (trials 1-5) scores. Adopting a serial recall strategy versus a semantic strategy could require TBI participants to utilize other cognitive resources to achieve comparable total learning scores.

As diffuse or traumatic axonal injury is the most frequent neuropathologic observation following mild TBI of all etiologies, it has been speculated that disrupted connection between frontal-subcortical networks could explain deficiencies in cognitive performance (Becker & Lim, 2003; Ghajar, Ivry, & Consortium, 2008; Hartikainen et al., 2010; Zappalá & Trexler, 1992). This hypothesis was recently examined using functional magnetic resonance imaging in TBI participants (mild-severe) during performance of a list-learning paradigm (Strangman et al., 2008). Participants were imaged under three list-learning conditions, two of which involved semantically related word-lists. On the final "directed" condition, participants were instructed on the use of a semantic clustering strategy. Findings revealed that during the directed semantic clustering condition, both TBI and control groups displayed improvements in recall, but that controls demonstrated increased coupling with activation observed in dorsolateral prefrontal cortex (DLPFC) and angular gyrus (AG) while the TBI participants did not. This was offered as evidence of a failure to coordinate processes in the DLFPC, "when and only when" directed to use a semantic strategy (Strangman et al., 2008). These findings were interpreted as indications of variable disruptions along the superior longitudinal fasciculus (SLF) connecting angular gyrus and DLPFC. The authors speculated that while the TBI participants did not engage the more efficient DLPFC-AG network, they still experienced improvements in learning by a separate processing network. These findings have particular relevance given prior report of a relationship between integrity of the SLF assessed via diffusion tensor imaging and behavior (Bendlin et al., 2008; Geary et al., 2010; Sidaros et al., 2009). From these works, the possibility is raised that dysfunction of the SLF in mild TBI may 1) underlie deficient higher-order strategy use, and 2) explain over-reliance on more externally derived strategy use.

While systematic higher-order strategy use facilitates learning and recall, if individuals are employing more externally-driven strategies or trying variable strategies, it appears intuitive that recall from trial to trial may be more random. Indeed, learning strategies in moderate-severe TBI have been

suggestive of a disorganized haphazard learning style coupled with an increased reliance on serial clustering (Deluca, Schultheis, Madigan, Christodoulou, & Averill, 2000; Millis & Ricker, 1994). Given our finding of a relationship with serial clustering and learning rate, we conducted a post hoc examination of words recalled consistently across trials. What proved most interesting were post hoc *t*-tests of independent means which revealed that the groups only differed significantly on consistency from trial 1 to trial 2, $t(61)=2.130$, $p=0.037$, but not on the remaining trials. Table 3 details these analyses.

[INSERT TABLE 3 HERE]

Recalling that our prior work focused on early learning inefficiency (Geary et al., 2010), a finding of less consistent recall across initial trials may be a plausible explanation of what may underlie trial 1 learning deficiency. Less consistent responding from trial 1 to two trial 2 may suggest that the mild TBI participants are responding to the second trial as if it were a novel list versus a repeated presentation (Delis et al., 2000) or possibly reflective of diminished attention (DeJong & Donders, 2010). This has also been offered as a theory to explain behavior in patients with frontal lobe dysexecutive syndrome (Roofeh et al., 2006; Stuss & Alexander, 2007). We also considered that our mild TBI participants might commit more intrusion errors reflective of reduced self-monitoring as has been argued by others (Busch, McBride, Curtiss, & Vanderploeg, 2005), but this was not the case ($p>0.05$) suggesting no source memory problems.

Study Limitations

In any TBI study, a primary concern is the inclusion of participants with a history of mild TBI without witness confirmation of LOC or PTA. Given the reliance on retrospective report, it is possible that some of these individuals did not sustain a TBI or sustained a TBI of greater than mild severity. In our sample, twelve participants reported no or unknown LOC.

Twelve TBI participants reported a history of multiple mild TBI. Primary CVLT-II trials 1-5, total learning, ListB and delayed memory analyses conducted with and without these participants demonstrated no change in the previously published findings (Geary et al., 2010). However, while comparisons of single versus multiple mild TBI participants detected no significant differences between

the TBI groups on variables of interest, the inclusion of individuals with multiple injuries raises the possibility that findings could be driven, in part, by changes attributable to multiple mild injuries as has been suggested by others (Weber, 2007). As such, future studies should be undertaken examining strategy use in a large group of patients with multiple mild TBIs so that the number of TBIs can be examined directly. Further, future studies would benefit by the collection of objective data on the duration of LOC and objective measurements of PTA for each injury. A prospective, longitudinal investigation of acute TBI course and recovery would achieve such aims.

As raised in our prior study, despite a high number of self-reported memory difficulties in our TBI patients, we did not collect any data regarding the functional significance of the initial learning deficiency or ask any questions particularly relevant to higher-order strategy use (e.g., "do you find it harder to organize information during your day-to-day?"). Future studies comparing strategy use and learning performance to more specific outcome variables would prove especially informative.

Despite these limitations, the clinical significance of reduced higher-order strategy use in mild TBI participants warrants further exploration. Given the continued debate regarding persisting cognitive deficits following mild TBI and the issues regarding the ecological validity and sensitivity of neuropsychological assessment to detect persisting cognitive changes in patients with a history of mild TBI (Iverson, 2010; Satz et al., 1999; Silver, 2000), this study endeavored to elaborate on the learning strategies of mild TBI participants. Specifically, while chronic memory dysfunction is not supported in the mild TBI literature, the issue may be one of what constitutes "memory" as standardly interpreted in neuropsychological evaluations. However, in daily interactions such as conversations, lectures, and work-place instructions, individuals are often presented with information one time, rather than being given the benefit of repeated "trials." Perhaps the chronic learning and memory difficulties reported by some mild TBI patients are related to reduced utilization of internally-driven strategies that facilitate learning and enhance recall. Given that strategy training has demonstrated improvements in learning and memory (Basso, Lowery, Ghormley, Combs, & Johnson, 2006; Fiszdon et al., 2006; O'Brien, Chiaravalloti, Arango-Lasprilla, Lengenfelder, & DeLuca, 2007; Schefft et al., 2008), these findings have

translation value in offering that mild TBI patients be given recommendations such as consideration of strategy use when learning information in order to potentially remediate learning inefficiencies.

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Figure Legend

Figure 1. **A.** CVLT-II raw recall findings across trials one through five for controls and patients with mild TBI. Statistically significant difference between groups was only observed on the first learning trial. **B.** Chance adjusted semantic clusters across trials one through five for control and mild TBI participants. Statistically significant differences between groups were only observed on trials three through five. **C.** Chance adjusted subjective clusters across trials one through five for control and mild TBI participants. No statistically significant differences between groups were observed between groups across trials. **D.** Chance adjusted serial clusters across trials one through five for control and mild TBI participants. No statistically significant differences between groups were observed between groups across trials.

Figure 1. CVLT-II raw recall and cluster analyses.

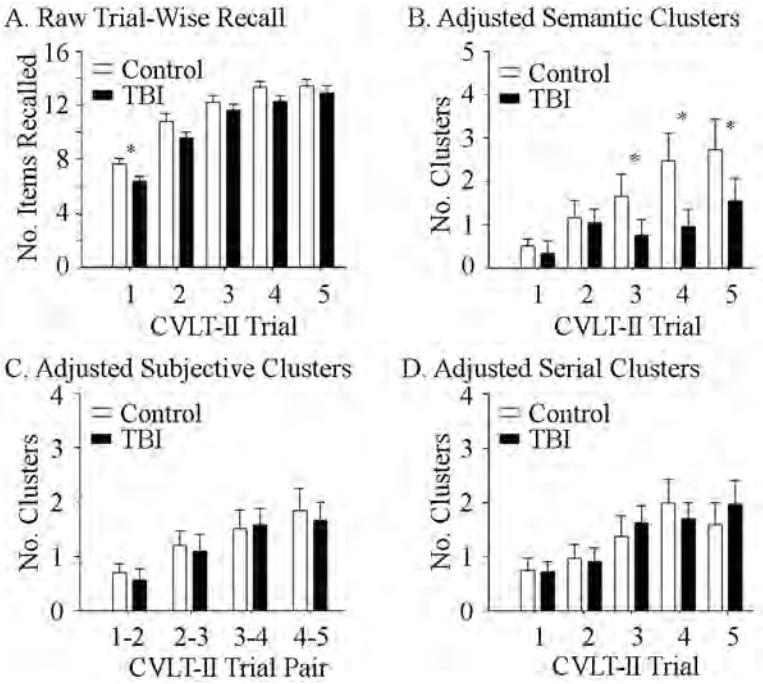
A. Raw Trial-Wise Recall
No. Items Recalled
Control
TBI
CVLT-II Trial
B. Adjusted Semantic Clusters
No. Clusters
Control
TBI
CVLT-II Trial
C. Adjusted Subjective Clusters
No. Clusters
Control
TBI
1-2
2-3
3-4
4-5
CVLT-II Trial Pair
D. Adjusted Serial Clusters
No. Clusters
Control
TBI
CVLT-II Trial

Table 1. Participant Demographics, Behavioral Data, and TBI Information

	Control (n= 28)		TBI (n= 35)		T-value	P-value
	Mean	SD	Mean	SD		
Demographic Variables						
Age	31.64	9.02	33.91	10.09	-0.93	0.356
Years of Education	15.79	1.73	16.37	2.09	-1.193	0.238
Years of Employment	12.05	9.86	16.24	10.25	-1.618	0.111
Hollingshead Highest Level of Employment	6.47	1.61	6.43	1.52	0.088	0.930
WTAR Full Scale IQ Estimate	110.21	11.40	110.54	9.67	-0.124	0.902
TOMM Trial 2	50.00	0.00	49.90	0.32	1.547	0.129
Dot Counting	8.60	2.50	9.07	2.49	-0.647	0.521
Employed/Student at Evaluation (% sample)	92.90%		94.30%			
Gender (M/F)	13	15	16	19		
TBI Variables						
Age at TBI (years)	-	-	28.54	10.81		
Time Since Injury (years)	-	-	5.63	6.57		
Length Loss of Consciousness (N=17) (minutes)	-	-	5.71	9.21		
Length of Post Traumatic Amnesia (N=10) (minutes)	-	-	33.50	26.98		
Current Cognitive Complaints (% sample)	3.60%		82.90%			
Current Behavioral Complaints (% sample)	3.60%		48.60%			
Returned to Work/School Following Injury (% sample)	-		94.30%			

Table 2. Correlation of Strategy Scores and Rate of Learning by Group

	Average Semantic Clustering	Average Subjective Clustering	Average Serial Clustering
Control	0.571**	0.560**	-0.061
Mild TBI	0.217	0.556**	0.476**

** sig $p<0.05$

Table 3. Consistency of Recall Across CVLT-II Trials

	Control (N=28)		Mild TBI (N=35)		T- Value	P-Value
	Mean	**sd**	**Mean**	**sd**		
Words Recalled T1-T2	6.32	2.37	5.14	2.02	2.130	.037
Words Recalled T2-T3	9.14	2.97	7.77	3.01	1.809	.075
Words Recalled T3-T4	11.00	3.14	9.83	2.88	1.540	.129
Words Recalled T4-T5	11.68	3.02	10.69	3.11	1.275	.207